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THE EVOLUTION OF THE PARALLEL SULCUS

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The great expansion of those areas of the brain which have been responsible for the evolution "of the high powers of intelligence that distinguish Man from all other living creatures" (13) renders the correct interpretation of many of the sulci a difficult matter. The foundation for the establishment of the homologies put forward in this communication is the original work of Elliot Smith on the *Sulcus Lunatus* in the Egyptian brain. Any topographical survey must start from two known points and, whereas the upturned end of the fissure of Sylvius provided one such point, the second only became available when he definitely fixed the homology of the sulcus lunatus and its attendant sulcus praelunatus. In a previous communication (14) I have described the occipital lobe in the Chinese from an examination of over 400 brains. The sulcus lunatus is found to be even more primitive in its form in this race than it is in the Egyptian. In addition to this large number of human brains, I have examined the brains of one Bornean bear, one baboon, twelve gibbons and fifteen orangs. This series provides practically every stage in the evolution of the parallel sulcus from the postsylvian condition to that found in man.

The establishment of correct homologies demands more than mere superficial resemblance in form, and here Elliot Smith, and later Brodmann[1], have given us the criteria of cortical structure, both macroscopic and microscopic (2, 3). Theoretically homology should not be regarded as certain until all the criteria are established. These criteria are the general form of the sulcus, its relationship with neighbouring sulci, its association with cortical areas and its phylogenetic and ontogenetic development (1). To these I have been able to add the relation of blood supply to cortical areas; for I have been able to determine that the vessels are so precisely arranged that the cortical areas can in most places be marked out by their distribution. This method has not been used in this investigation, though I have used it in the occipital region where it has been of value in confirmation.

In practice, however, one or other of the criteria may fail. In over 75 per cent. of cases the stripe of Gennari has been found to be limited by the sulcus lunatus; and yet there are cases in which the sulcus lunatus has its characteristic form, in which its relations with the praelunate and paramesial sulci are

[1] Brodmann's figures 104, 98, 90 and 85, omitting areas not having a direct bearing on the problem, have been reproduced as figs. 1, 2, 4 and 10 to save the reader having to refer to his original paper.

typical, and yet in which the stripe of Gennari falls short of the posterior lip of the sulcus. In such cases homology is justified, despite the failure of one criterion.

The present state of our knowledge demands the same scrutiny in homologising the other sulci of the brain.

Superficial resemblance in form would appear to have been the only criterion used in identifying the complex sulcus temporalis superior of human anatomy with the postsylvian or parallel sulcus of lower forms. It will be shown that the limits of that portion of the sulcus temporalis superior which is definitely homologised with the postsylvian sulcus are clearly circumscribed. It is a sulcus separating areas 21 and 22 of Brodmann; and is one of the most constant sulci of the brain. The sulcus temporalis superior, as described in textbooks, can be defined as a sulcus extending from the temporal pole to any point in the inferior lobule. It can be made to include many clearly defined sulci—the sulcus temporalis anterior, the parallel sulcus proper, the sulcus which arches over the upturned end of the fissure of Sylvius in the Apes, the sulcus angularis, both limbs of the anterior occipital sulcus and sometimes the praelunate and part of the lunate sulcus. On account of the confusion attendant upon homologising such a series of sulci with the clearly defined parallel sulcus of lower forms the term sulcus temporalis superior will not be employed in this paper.

The evolution of the parallel sulcus plays a very important part in the evolution of parietal area, which has been the subject of close analysis in the interpretation of endocranial casts of fossil man, and in the localisation of those higher intellectual functions associated with the speech in the higher sense of the word. The correct topographical survey of this area, therefore, assumes an added importance in the light of the more recent advances in our knowledge of cerebral localisation.

It is convenient to describe the evolutionary changes which have taken place in arbitrary stages. It is important to appreciate, however, that even in the same groups there are no hard and fast lines of demarcation.

Stage 1. In the Carnivora we have a combined suprasylvian postsylvian arc. This condition is also found in *Daubentonia* but in no other Primate. The separation of the two elements of the suprasylvian postsylvian arc takes place very early in the evolution of the Primates. The identity of the postsylvian element with the parallel sulcus has been established by Elliot Smith who says, "By far the most significant feature of these brains of the Aye-aye is the existence of a separate suprasylvian arc. In the Carnivora and many other mammals (e.g. *Bradypus*) the suprasylvian sulcus is joined to the postsylvian (generally known as 'posterior suprasylvian') to form a 'suprasylvian arc.' Such an arc is generally found in the brain of *Daubentonia*, but in that of no other Primate. In all the Lemurs and Apes the suprasylvian sulcus is separated from the postsylvian (which is then called 'parallel' or 'superior temporal') sulcus (4)."

Brodmann has investigated the cortical areas in *Cercoleptes*. His figure 104 (fig. 1) shows the postsylvian as a sulcus which lies between areas 21 and 22. Area 21 extends to a higher level than area 22 and is separated from area 19 posteriorly by the sulcus postlateralis (3).

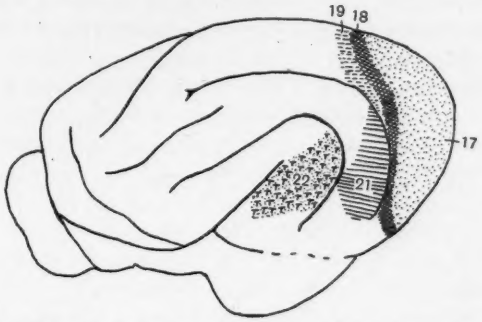

Fig. 1. Taken from Brodmann's fig. 104 to show the relationship of areas 17, 18, 19, 21 and 22 to the postsylvian sulcus.

In the further evolution of this region, area 21 becomes pushed downwards into the temporal region.

Stage 2. This stage is characterised by the downward displacement of the area 21 and by the extension of the parallel sulcus into area 19. It is best illustrated in the brain of the Lemuridae (fig. 2). It is reasonable to suppose that the lemuroid ancestor possessed the type of suprasylvian arc seen in the Chiromyidae (4).

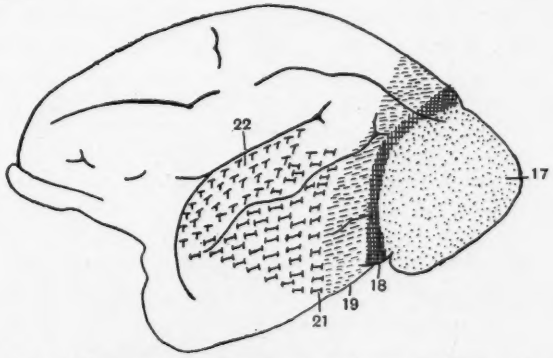

Fig. 2. Taken from Brodmann's fig. 98 to show the relationship of areas 17, 18, 19, 21 and 22 to the parallel sulcus.

If the cortical areas of the Lemur are compared with those of *Cercoleptes* it will be seen that area 19 has expanded to a greater extent in the former. It is only in its lower part that the parallel sulcus limits the areas 21 and 22, whilst superiorly it crosses the line previously occupied by the sulcus post-

lateralis to extend into area 19. I have not had the opportunity of examining the brain of a lemur, but from the close resemblance of the parallel sulcus in this form with that in the Cercopithecidae (see Stage 3), I am inclined to regard the uppermost part of the parallel sulcus in the lemur as a new sulcus formed in the line of the postsylvian sulcus in much the same way as the anterior temporal sulcus tends to join the anterior end of the parallel sulcus in the orang and in man.

Stage 3. The general form of the sulci in the Cercopithecidae (fig. 3) is

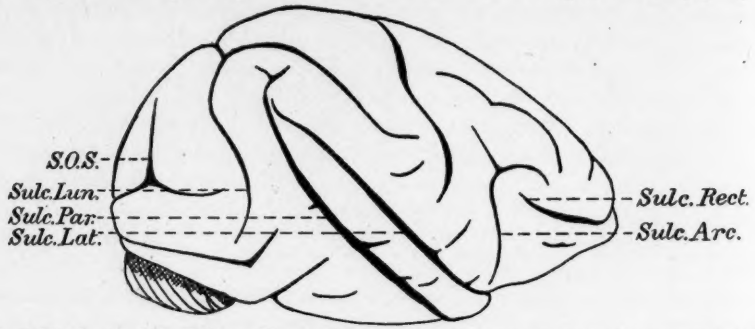

Fig. 3. The brain of the Baboon. The parallel sulcus closely approximates to the upper end of the fissure of Sylvius. With its depths the lower segment is separated from the upper segment by a deep annectant gyrus. The sulcus arcuatus is separate from the sulcus rectus. No sulcus praelunatus is present.

very similar to that seen in the Lemuridae. Certain new sulci have made their appearance. In the frontal lobe the sulcus arcuatus and the sulcus rectus are defined. The sulcus lunatus makes its appearance immediately anterior to the area striata. The parallel sulcus extends from the temporal pole to the gyrus lying in the angle between the lunate and interparietal sulci. Inferiorly the parallel sulcus lies between areas 21 and 22 (fig. 4). Superiorly

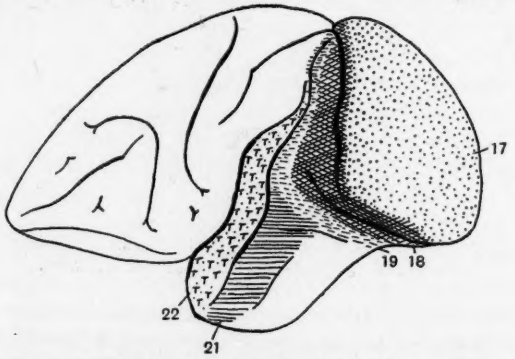

Fig. 4. Taken from Brodmann's fig. 90 showing the shifting downwards of area 21 and the relationship of the cortical areas to the sulci.

it lies immediately anterior to the area 19 or area peristriata. The area 21 has been pushed downwards as compared with the lemuroid condition.

If the parallel sulcus is opened up in the Cercopithecidae it will be found that it consists in reality of two elements. The two elements are separated by a deep annectant gyrus. The lower element ends in close proximity to the highest point of area 21. The inferior extremity of the upper element may sometimes appear on the posterior border of the main sulcus at the level of the deep annectant gyrus. This occurs on the right side of my specimen as seen in fig. 3. The inferior element of the parallel sulcus is the only portion of the sulcus which is strictly homologous with the postsylvian sulcus of lower forms. It retains the same form and relations throughout the whole of the Anthropoideae.

In marked contrast with the fixity of the inferior element the superior element undergoes a progressive series of changes, extruding sulci from its posterior wall in much the same manner as the sulcus lunatus extrudes in turn the parieto-occipital, the praelunate and paramesial sulci, and the sulcus occipitalis transversus.

Stage 4. This stage is the key to the correct interpretation of all the stages leading to the human condition (fig. 5). The features of the parietal lobe of the gibbon fully justifies its inclusion in the family Simiidae, for all the essential changes which are to occur in this region are foreshadowed.

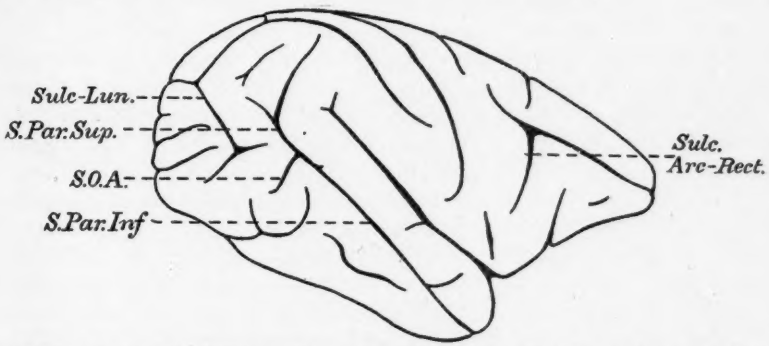

Fig. 5. The brain of the Gibbon. The parallel sulcus is extruding the two segments of the anterior occipital sulcus. The sulcus praelunatus is present. The arcuate-rectus complex has the simple form of the Cebidae. The presence of the sulcus temporalis anterior is indicated.

The outstanding feature of the gibbon's brain is the extent of the differentiation of the parietal region in contrast with the primitive simplicity of pattern in the frontal region. The differentiation of the arcuate-rectus complex has progressed no further than the condition seen in the Cebidae. The two sulci are concurrent, although their separate character is seen on opening up the lips of the arched sulcus.

The differentiation of the parietal region has progressed to such an extent that it is directly comparable with the simpler types seen in the Orang utan (fig. 6). The lunate sulcus assumes a characteristic form, accentuated by the presence of the sulcus praelunatus. In all my specimens there is no variation in the form and relations of the lunate sulcus. The most significant change brought about by the expansion of cortex, which produces the sulcus praelunatus, is seen in the extrusion from the parallel sulcus of the sulcus mentioned in the brain of the baboon. This sulcus is directed downwards and backwards and lies more or less parallel with the recurved lower extremity of the sulcus lunatus. Its point of exit marks the upper end of that portion of the parallel sulcus which corresponds with the postsylvian sulcus of lower forms. Areas 21 and 22 have taken up the position which they retain throughout the whole of the Simiidae. I propose to name this fixed element the *inferior parallel sulcus* to distinguish it from those new sulci which are to make their appearance anteriorly and posteriorly. Already in the gibbon the presence of the anterior temporal sulcus is indicated. This sulcus comes into being on the development of the area temporalis polaris of Elliot Smith; it tends to become confluent with the anterior end of the inferior parallel sulcus, but, as Elliot Smith has shown, is distinct from it. The superior parallel sulcus is unstable owing to the fact that it lies within the area in which the greatest development is taking place. These three elements, the anterior temporal, the inferior parallel and the superior parallel, are indicated in fig. 243 of the Catalogue of the Royal College of Surgeons (5). The anterior temporal sulcus is not marked. The parallel sulcus is marked in two places, the inferior of these points to the inferior parallel sulcus, the superior to the superior parallel sulcus.

The individuality of these three sulci is often demonstrated by their remaining distinct. This is indicated diagrammatically in Cunningham, fig. 594 (2). It is the condition seen in the embryo at six months (10, 11, 12).

The evolution of the parietal lobe finds its expression in the succession of changes which occurs in relation to the sulcus lunatus and the superior parallel sulcus. In another paper I have traced the changes which take place in relation to the sulcus lunatus; and just as the sulcus lunatus is an opercular sulcus gradually unrolling itself and extruding from its anterior wall hidden sulci, so also the same expansion which has revealed these sulci causes the extrusion of a series of sulci from the posterior wall of the superior parallel sulcus, in addition to the formation of a new compensatory sulcus angularis.

The lower end of the buried sulcus seen in the baboon comes to the surface in the gibbon, and in many cases an extruded branch is seen lying superiorly to the sulcus praelunatus. These two branches, when completely extruded, will be found to be the upper and lower segments of the sulcus occipitalis anterior.

The upper end of the superior parallel sulcus belongs to the gyrus supramarginalis and normally ends by arching over the upturned end of the fissure of Sylvius—a mode of termination best seen in the gorilla.

The brain of the orang shown in fig. 6 belongs to the fourth stage in the evolution of the parietal area, but, in marked contrast with the condition found in the gibbon, the frontal area has increased greatly in size. The form of the sulci in this region would seem to indicate that the sulcus precentralis inferior is a new sulcus formed behind the sulcus arcuatus and the sulcus rectus which here retain the simple form seen in the baboon.

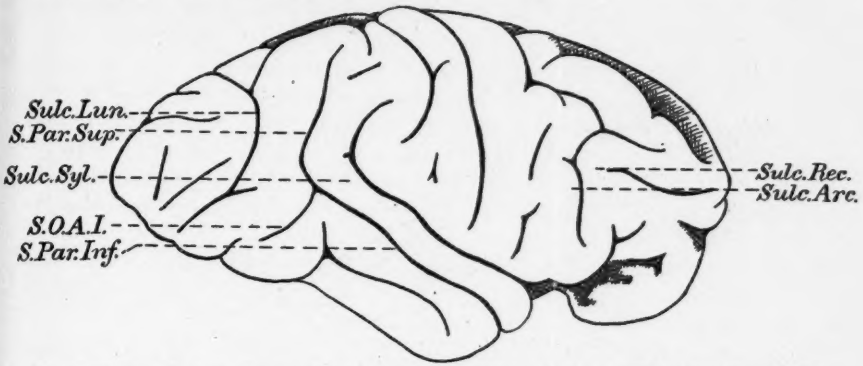

Fig. 6. The brain of the Orang. The lower segment of the anterior occipital sulcus lies parallel with the recurved limb of the sulcus lunatus. The upturned end of the superior parallel sulcus tends to curve over the upper end of the fissure of Sylvius. The form of the inferior parietal lobule is very similar to that shown in fig. 2, in contrast to the more advanced condition of the frontal lobe. The arcuate and rectus sulci are clearly seen.

Stage 5. I have no specimen which so well illustrates this stage as that of the chimpanzee depicted in Quain, fig. 288 (6). The sulcus occipitalis anterior is almost extruded. Its relations are so clear that no comment is necessary.

Stage 6. This stage is remarkably shown in figs. 7, 9 and 10. Fig. 7 is the brain of an orang utan, figs. 9 and 10 are Chinese. The brain of the orang figured might well be called most human-like and the human brains most ape-like. They are even more primitive in form than the brain depicted by Elliot Smith (fig. 17 in his *Essays on the Evolution of Man*) (13).

In fig. 7 the upper and lower extremities of the anterior occipital sulcus, which make their appearance first in the gibbon (fig. 5), and which appear in the same form in many of my orang brains, have now become completely extruded. The anterior occipital sulcus is now a definite entity. It lies parallel with the sulcus lunatus and forms the anterior boundary of the prae-occipital area. The backward movement of the lower limb of this sulcus is an expression of the extent of the development of that area of the cortex which Brodmann numbers 39 in man (fig. 8); or perhaps it would be more accurate to say for the moment, since I have no evidence that area 39 develops in the orang, that this expansion foreshadows the human condition. Further evidence of the extent of this expansion is seen in the development of the compensatory sulcus lying between the superior parallel sulcus and the upper limb of the anterior

occipital sulcus. This new sulcus is the sulcus angularis—the independent nature of which has already been pointed out by Elliot Smith.

One other very constant sulcus deserves mention. This sulcus is the short connecting sulcus lying between the superior parallel and anterior occipital sulci, and it is of use in identifying sulci in the Chinese brain. It seems to be

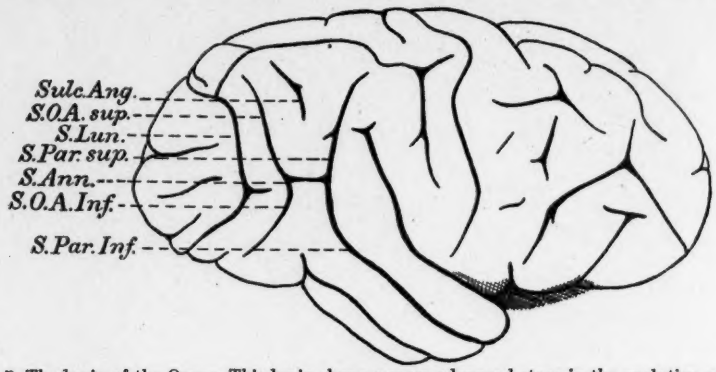

Fig. 7. The brain of the Orang. This brain shows a more advanced stage in the evolution of the inferior parietal lobule than the brain shown in fig. 3. The whole of the sulcus occipitalis anterior has emerged from the superior parallel sulcus and is connected with it by the sulcus annectans. The sulcus angularis has made its appearance.

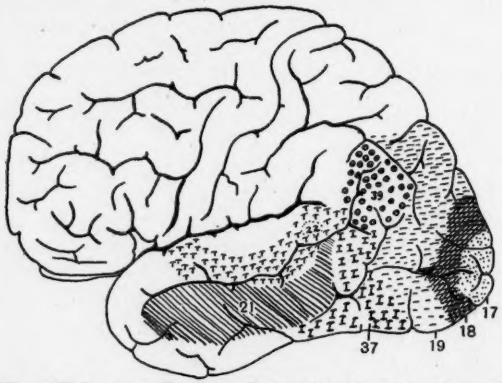

Fig. 8. Taken from Brodmann's fig. 85 to show the relationship of areas 21 and 22 to the parallel sulcus.

produced by the expansions of the cortex above and below it, and is therefore of the nature of a compensatory sulcus similar to the sulcus praelunatus. For descriptive purposes I propose to name it the sulcus annectans, although I regard it as a component part of the anterior occipital sulcus.

Figs. 9 and 10 completely confirm the interpretation of the changes which have taken place. All the sulci are present in recognisable form. In fig. 10

the upper end of the superior parallel arches over the upturned end of the fissure of Sylvius in typical gorilla-like fashion. In fig. 9 this element has become detached and lies in the gyrus supramarginalis. This is the more usual

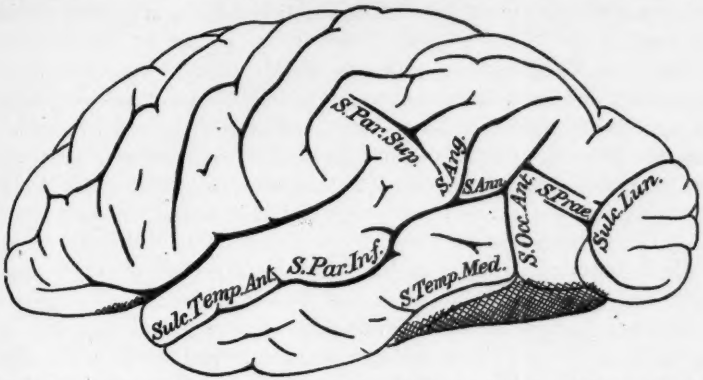

Fig. 9. The brain of a Chinese. The upper portion of the superior parallel sulcus has broken away and is seen in the gyrus supramarginalis. The sulcus angularis is joined to the proximal end of the sulcus annectans. The sulcus occipitalis anterior bounds the area praeoccipitalis anteriorly. The sulcus lunatus is very extensive with a well-marked sulcus praelunatus.

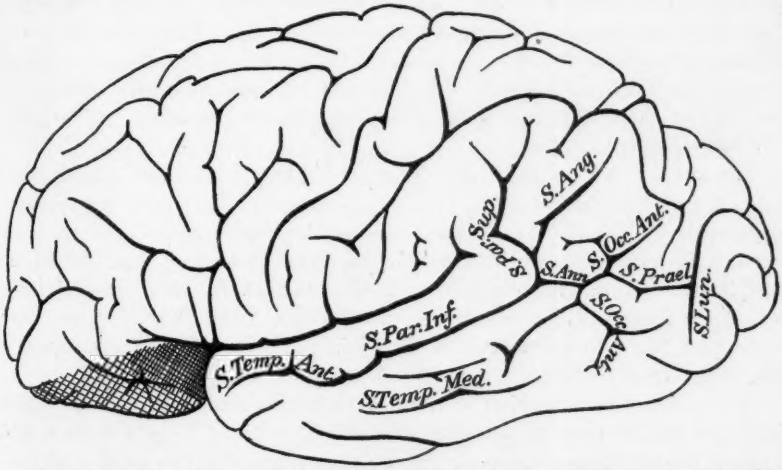

Fig. 10. Chinese brain. The superior parallel sulcus arches over the fissure of Sylvius. The angular sulcus joins the superior parallel sulcus close to the origin of the sulcus annectans. The upper segment of the anterior occipital sulcus is joined by the sulcus praelunatus. Fragmentary medial temporal sulci join the inferior segment of the same sulcus.

human condition. The anterior occipital sulcus, still retaining its relation with the prae-occipital area, connects with the parallel sulcus through the sulcus annectans. The expansion of area 39 has developed the sulcus angularis to

such an extent that it joins the sulcus annectans at the point where the triradiate sulcus lying in the gyrus supramarginalis has broken away. The identity of the detached portion and its homology with the forwardly curved superior parallel sulcus in the gorilla is established in fig. 10. Every variation of the sulci in the inferior parietal lobule is explainable by the above interpretation of the homologies, taking into consideration at the same time that compensatory sulci may be formed and join with the interparietal sulcus.

In fig. 9 the lower end of the sulcus occipitalis anterior is joined to a well-developed sulcus temporalis medius. The usual description given in text-books, originated without due regard to morphological facts, could be applied to this specimen. The sulcus temporalis superior is most commonly described as being the homologue of the parallel sulcus and ending in the angular gyrus. The middle temporal sulcus is diagrammatically represented as lying parallel with the sulcus temporalis superior and ending in the gyrus postparietalis. The detached portion of the superior parallel sulcus is disregarded or unrecognised. It is now clear that the superior temporal sulcus so described is a complex sulcus consisting of the anterior temporal (related to the area temporalis polaris), the inferior parallel (related to areas 21 and 22), a portion of the superior parallel and the angular sulcus (related to area 39), with in some cases—depending upon the point of junction of the sulcus angularis—the sulcus annectans. Further, when the angular sulcus is separate, the upper segment of the anterior occipital sulcus may be included. The middle temporal sulcus so described consists of a series of disconnected sulci (the proper middle temporal sulcus), occasionally joined together, connecting with the lower segment of the anterior occipital sulcus and thence continued to the post-parietal lobule.

One other sulcus plays its part in obscuring the picture, and especially so when the identity of the sulcus lunatus is uncertain. The sulcus praelunatus, apparently coming under those influences which produce the sulcus annectans, extends forward into the inferior parietal lobule and may join the sulcus occipitalis anterior. This often occurs at the point where the sulcus occipitalis anterior is joined by the sulcus annectans. Elliot Smith and Kappers both state that the sulcus praelunatus may join the sulcus temporalis superior. The meaning of this is now apparent (8).

The series of brains which has been used in this communication has been ideal for the purpose of morphological interpretation. I do not, however, propose to enter into a discussion on the departures from this ideal condition, for such a discussion has recently been made by Wang and Kappers on a large series of Dutch brains (9). An examination of their valuable contribution convinces one of the validity of the argument set out above. By regarding the sulci marked "Ascending i, ii and iii" by these authors as the upper part of the superior parallel sulcus, the angular sulcus, and the upper segment of the anterior occipital sulcus respectively their description of the parietal region gains in morphological significance.

The embryological evidence is present in the works of Retzius, Kolliker, and Keibel and Mall and the following figures are referred to in particular: Kolliker (10), fig. 359; Keibel and Mall (11), fig. 79; Retzius (12), Tafel IX, fig. 8; Tafel XIX, fig. 5 and Tafel XXIV, fig. 4.

In conclusion I have to express my deep sense of gratitude to all those who have given me the material which has made this work possible. The particular brain which forms such an interesting link (fig. 7) was given to me by Dr Le Gros Clark. For other specimens of orang and gibbon brains I have to thank Mrs Le Sueur and Mr Banks of Sarawak, and Mr Boden Kloss and Mr Chasen of Raffles Museum, Singapore.

SUMMARY

1. The relation of the parallel sulcus to certain cortical areas has been discussed.

2. That portion of the parallel sulcus which borders areas 21 and 22 is homologous with the postsylvian of lower forms.

3. The upper portion of the parallel sulcus arches over the upper end of the fissure of Sylvius in many human brains and is named the superior parallel sulcus.

4. The angular sulcus is a compensatory sulcus produced by the expansion of the cortex forming area 39.

5. The anterior occipital sulcus with its sulcus annectans is recognised as a very definite entity bounding the area prae-occipitalis.

6. A discussion of the bearing of the morphological facts on endocranial casts and cerebral localisation is not here entered into.

ABBREVIATIONS IN FIGURES

Sulc. Ang.	Sulcus Angularis.
S. Ann.	Sulcus Annectans.
Sulc. Arc.	Sulcus Arcuatus.
Sulc. Lun.	Sulcus Lunatus.
S. Par. Inf.	Inferior Parallel Sulcus.
S. Par. Sup.	Superior Parallel Sulcus.
S. Prael.	Sulcus Praelunatus.
S. Occ. Ant.	Sulcus Occipitalis Anterior.
S. O. A. Sup.	Sulcus Occipitalis Anterior (upper element).
S. O. A. Inf.	Sulcus Occipitalis Anterior (lower element).
S. O. S.	Sulcus Occipitalis Superior.
Sulc. Rec.	Sulcus Rectus.
Sulc. Temp. Ant.	Sulcus Temporalis Anterior.
Sulc. Temp. Med.	Sulcus Temporalis Medius.

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THE BLOOD SUPPLY OF THE HYPOGLOSSAL NUCLEUS[1]

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INTRODUCTION

An investigation into the blood supply of the Claustrum (1) opened up a critical problem in arterial distribution. Both Duret (2) and Beevor (3) considered that the claustrum was supplied by the cortical vessels supplying the cortex of the Island of Reil and that no arterial anastomosis took place between these vessels and those supplying the lenticular nucleus. In 1920 I found that, on tying off the cortical supply and on injecting the proximal segment of the middle cerebral artery, the claustrum and the lenticular nucleus were both injected with the same colour and further that there was no anastomosis between the claustrum and the cortex of the Island of Reil. I was next able to inject the claustrum so that on the one side no anastomotic invasion of the lenticular nucleus took place and on the other side no invasion of the cortex. The findings of Duret and Beevor were thus reconciled with my own.

The critical problem which presented itself was, Why should not the capillary areas between these three structural units be opened up to form arterial channels? If the arterial distribution is merely a matter of mechanical convenience it would be reasonable to suppose that it would be more convenient for the cortical vessels to supply the claustrum than for this structure to be supplied by its own vessels. Furthermore the constancy of distribution is a phylogenetic one and serves definite functional needs.

It became evident that before the principles underlying blood vascular distribution could be determined the exact distribution of the arteries in the region of their final supply had to be worked out. The method of analysing the nerves into their final components had to be applied to the analysis of the arterial distribution.

Previous work on the development and distribution of arteries has, for the most part, been confined to the larger distributing trunks—the aorta, the vertebral artery and the like. The result of this work has led to the conception that arteries are variable in a haphazard manner. If, however, we turn to the works of Beevor and Stopford on the blood supply of the brain, where the distribution is considered in relation to the organ supplied and where the exact course of the supplying artery is not so fully dealt with, we find a remarkable precision in blood supply. There is a definite vascular autonomy in certain areas and the question again presents itself—Why should not arterial anastomoses occur between these autonomous areas of supply?

[1] For being in a position to publish this paper and that on "The arteries of the brain of the Orang Utan" I have to express my indebtedness to the University of Hongkong.

In another communication (1), I have advanced the hypothesis that these areas are areas of definite function; that arteries are laid down in response to functional demands, and that they are phylogenetically and ontogenetically constant. The hypothesis appears to be sufficient to explain the distribution to structures arising segmentally or having segmental function as in the case of the hypoglossal nucleus. The supply to structures of intersegmental and suprasegmental value is more difficult to interpret in the present state of our knowledge. With the advent of intersegmental and suprasegmental function the segmental arteries of the body become linked up at different levels of function by longitudinal anastomotic channels. Strictly speaking, these new formed channels do not supply structures directly, but indirectly by vessels which were previously laid down. The dorsal segmental artery supplies all the elements of the segmental reflex arc. The vertebral artery is a longitudinal channel formed at this level of function and so indirectly supplies receptor, intercalator and expressor organs. The longitudinal anterior spinal artery is formed at the level of effector function and so indirectly supplies effector nuclei through the segmental anterior spinal arteries. The analysis of blood distribution must be in terms of these final arteries. The anterior spinal arteries may arise from the longitudinal anterior artery or from the vertebral direct; from the point of view of functional value the supply is the same.

The difficulty arises in explaining the arterial supply of the intersegmental and suprasegmental structures of the brain which appear at the same time as the intersegmental longitudinal anastomoses. The Betz cells of the motor cortex and the fibres of the pyramidal tracts are functional units and their blood supply is multiple. In the medulla oblongata the internal area of Flechsig, including the pyramidal tract, is supplied by the anterior spinal artery and is an autonomous vascular area. In the communication mentioned above the opinion was expressed that on more discriminating work being done on the blood supply of the medulla oblongata an explanation might be forthcoming of the hypoglossal nucleus and the pyramidal tracts being supplied by the same artery. I felt that it might be possible to separate out subordinate vascular areas within the main autonomous vascular internal area of Flechsig in the same way as the claustrum was separated from the lenticular nucleus and the cortex. The method of injection gives a varying picture owing to different degrees of completeness of the operation. The specimen to be described shows a very clean cut separation of the basilar and tegmental portions of the pons Varolii and it is recorded in the same spirit as one would record a single case of arterial occlusion.

MATERIAL AND METHOD

The brain is that of an adult Chinese male. The anterior spinal artery was injected by inserting a cannula into the vertebral artery proximal to the origin of the anterior spinal artery and by tying off the vertebral artery immediately

distal to it. The posterior inferior cerebellar artery was injected with a different colour; the injection of this vessel was, however, unsuccessful.

I have to thank Mr Li Sau Cho for the accurate drawings which are produced. The line of section is shown in Plate I, figs. 1 and 2. It will be seen that they are not quite transverse, which tends to exaggerate the features about to be described.

GENERAL DESCRIPTION

Plate I, fig. 1, shows the floor of the fourth ventricle after injection of the anterior spinal artery. On comparing this picture with that of Stopford's fig. 7 (4), the resemblance is so striking as to fully confirm his statement—"Invariably the trigonum hypoglossi was accurately defined by the stain of the injection." There is, however, an important difference in the two specimens, for in my specimen the injection involves the whole extent of the trigonum hypoglossi and even a small portion of the abducens nucleus. Stopford found that under no circumstances did the anterior spinal artery supply any region above the lower border of the pons. If the anterior spinal artery arose at an unusually low level or if there was extreme caudal fusion of the two vertebrals the level of the upper limit of supply of the anterior spinal artery was affected. In other words the vertebral and anterior spinal arteries are to a great extent interchangeable as far as the supply of the median somatic motor nucleus is concerned. In the specimen shown in fig. 1, the cephalic extension of the injection as far as the abducens nucleus was due to the anterior spinal artery and not to the vertebral artery; for there is no involvement of the vagal area. If we regard the vertebral artery as an intersegmental channel there is no contradiction in our results and the blood supply gains in meaning, for then all arteries supplying the hypoglossal nucleus are segmental anterior spinal in character. The variations are merely a matter of whether the segmental stems of the anterior spinal arteries remain with the vertebral or whether they disappear, with the exception of the main stem of the longitudinal anterior spinal artery.

The differentiation of the blood supply of the medulla oblongata necessitates the study therefore, not of the vertebral artery, but of the value of its branches. Stopford and Beevor obtained their discriminating results because their work was in the main concerned with the final vessels of distribution and not with the intersegmental longitudinal anastomoses.

Plates I and II show the internal distribution of the injection. No comment is called for on those sections caudal to the lower border of the pons Varolii for they correspond almost exactly with those of Stopford. Above this level, however, it is seen that the spread of the injection has separated off the tegmental from the basilar portion of the pons. The branches of the anterior spinal artery which supply the median somatic motor area above the level of the lower border of the pons have entered the foramen caecum of Vicq d'Azyr. Stopford's fig. 20 shows that this area was supplied by the basilar

artery. If we apply the principle of regarding an arterial supply in terms of the final components of that artery, the basilar artery becomes a longitudinal commissural anastomotic channel linking up vessels of equal function homologous with those vessels arising from the vertebral artery.

Thus we have median somatic motor arteries, lateral intercalated or radicular arteries and rhombic or cerebellar arteries arising from either the vertebral or basilar arteries. Furthermore these vessels are interchangeable within their own functional areas. In the same way as the cerebellar arteries may arise from either the basilar or vertebral artery so also in this case the main supply of the median somatic motor nucleus has arisen from the anterior spinal artery. In the communication already referred to, I pointed out that longitudinal anastomoses took place between vessels of equal function, and in this specimen it seems reasonable to postulate that the longitudinal anastomosis within the area of the effector function extends more cranially than usual.

The clean cut nature of the junction between the basilar and tegmental regions of the pons would seem to indicate that these two regions belong to two functionally different vascular systems; and that it may be possible to subdivide the arterial supply of the medulla and pons into subordinate autonomous areas.

Stopford remarks that "more failures have occurred in the injection of this artery (the basilar) than in any of the others." It would be of interest to know whether this failure was more marked in the median somatic motor areas.

In conclusion I would emphasise that, whilst the appearance of the specimen above described is most suggestive from the functional aspect, in the light of what I have previously written, the results of injection are subject to a considerable degree of variation and the specimen can only be regarded as one case, with the value of one case of described arterial occlusion.

DESCRIPTION OF PLATES

Plate I, figs. 1 and 2. Drawings of the pons and medulla oblongata illustrating the appearance of the floor of the fourth ventricle after injection of the anterior spinal artery and showing the line of the sections illustrated in Plates II and III.

Plates II and III. Sections of the pons and medulla oblongata illustrating the internal distribution of the anterior spinal artery.

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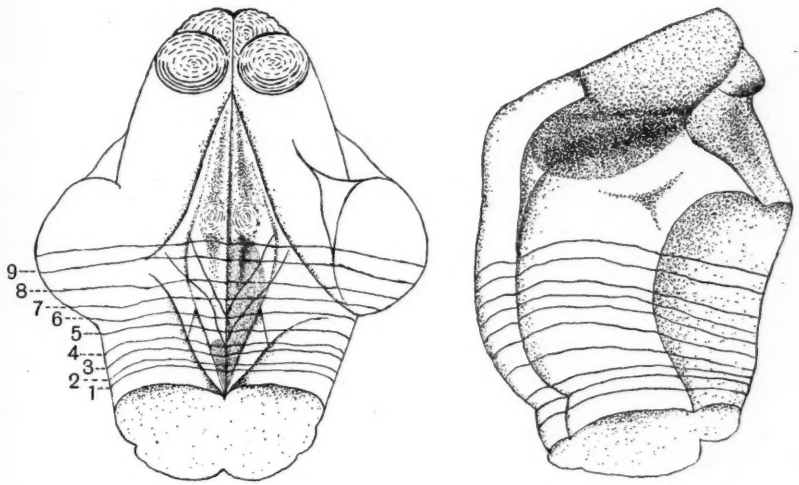

Figs. 1 and 2. Showing the floor of the fourth ventricle after injection of the anterior spinal artery and the line of section of the pons and medulla.

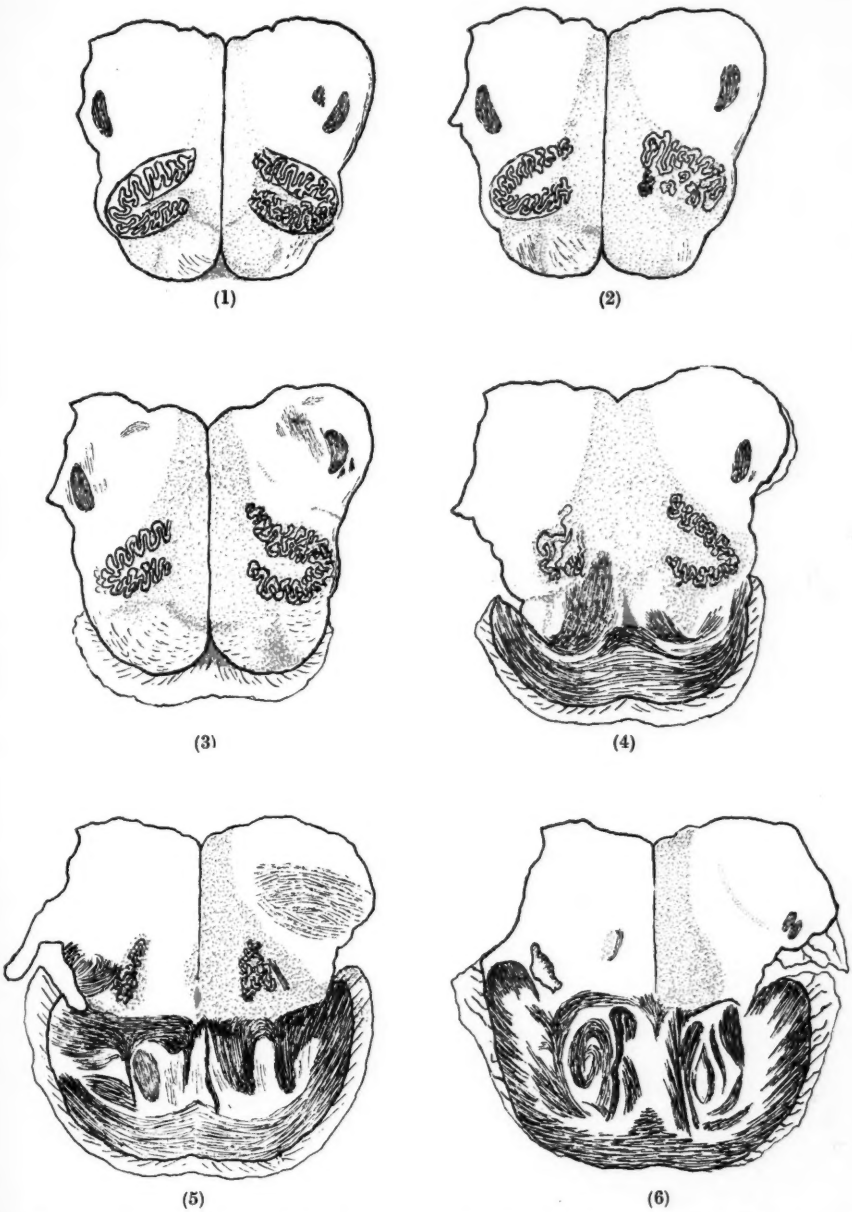

Fig. 3. Sections through lines 1, 2, 3, 4, 5 and 6 showing the sharp line of demarcation between the basilar and tegmental portions of the pons.

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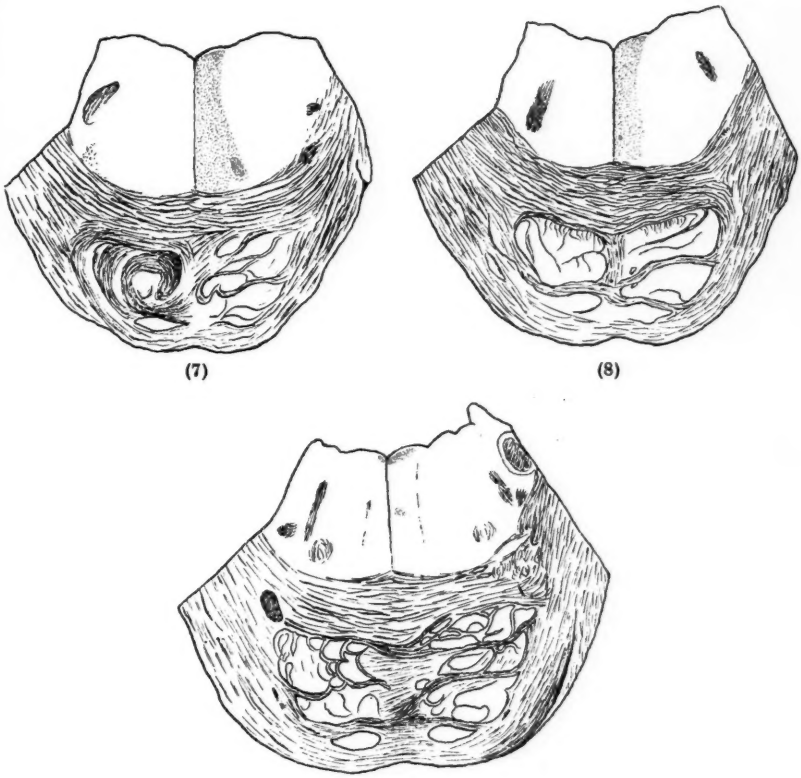

(7) (8)

(9)

Fig. 4. Sections 7, 8 and 9.

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THE NATURE OF THE STRUCTURAL CHANGES IN NERVE ENDINGS IN STARVATION AND IN BERI-BERI

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Most authors who have considered the relation of beri-beri to inanition record their opinion that inanition alone does not produce beri-beri. In this inability to reproduce the disease by starvation alone those who see a close parallel between beri-beri and the various forms of toxic neuritis find their best ground for believing that beri-beri is a similar disease.

That inanition does reproduce in birds a condition indistinguishable during life from beri-beri and with a similar pathology of the nervous system has been claimed by Chamberlain, Bloombergh and Kilbourne (1) and also by Eijkman and van Hoogenhuyze (2). The latter specifically states that the sciatic nerves show a similar myelin degeneration to that found in the polyneuritis induced by feeding the deficient diet. In addition, Eijkman claimed that if, during the food deprivation, the birds were "drenched" with water, the symptoms were produced much more rapidly.

Most of the pathological investigations of beri-beri have been carried out either in birds or in man. Kimura (5) has recently made an important and extensive investigation of the degenerative and regenerative changes occurring in rice-fed pigeons. The diet of polished rice is, however, so defective in proteins, fat and salts that one hesitates to apply in detail the results so obtained to experimentally induced beri-beri in mammals. A survey of the literature discloses that there are a number of points relating to the pathology of the disease that have not been adequately decided. The disease has been conceived as a general involvement of the nervous system (Vedder (8)); or as disease of the motor cells of the spinal cord (McCollum and Simmonds (7)). Findlay (3) sees in the chromatolytic changes in the nerve cells the basis of the pathology of the disease. Again, it has been regarded as a peripheral neuritis, but no precision has been reached as to what nerves or what portions of the nerve trunks are chiefly involved. Finally, the disease has been looked on, not as a specific affection of the nervous system, but as a condition characterised by a failure of growth and development.

The involvement of the sensory nerves has been a matter of inference or assumption rather than resting on any examination of the nerves themselves. Reference to the sympathetic nervous system are of a similar nature. Lesions are attributed to this system rather on the basis of certain symptoms than on the actual observations of the cells and fibres. The state of this system is

of some importance since it has been shown that the adrenal undergoes hypertrophy in beri-beri (McCarrison (6) and Kelleway (4)) and inanition (McCarrison (6) and Findlay (3)).

The fact is often mentioned (Vedder (8), Voegtlin and Lake (9), and others) that the myelin degeneration bears no relation to the symptomatology of the disease. The immediate recovery from the disease after the administration of the vitamin (cats 12 hours, Voegtlin and Lake (9), McCarrison (6) and others in birds) is a difficult observation to reconcile with any profound changes in the nervous system.

The objects of the present investigation were to determine, if possible, the point at which the degeneration began in the nervous system; to find out what changes occurred in the sympathetic portion of the autonomic nervous system; to study as well the changes, if any, in the peripheral nervous system that occur in animals deprived of food. At the same time the histology of the ductless glands was observed.

MATERIAL AND METHODS

This communication is part of an investigation that is being carried out by Professor Drummond[1] of the Department of Biochemistry of University College. He has very kindly provided me with all the material used in this report. The observations presented here are confined to rats. Professor Drummond placed at my disposal three series of rats. The first were animals that had been fed on a deficiency diet and had developed beri-beri. The diet consisted of: caseinogen 20 parts, rice starch 65 parts, salt mixture 5 parts, cod-liver oil 2 parts, hardened oil 10 parts. Some of the animals were only slightly affected, others were moribund. A second series were rats that had been allowed to drink at will, but had been deprived of all food for a period varying from four to seven days. A third series comprised rats that had been kept under similar conditions to the second group but had been allowed to nibble a yeast extract at will.

A considerable number of histological methods were used. Some were investigated by the Marchi method. These were first injected through the aorta with equal parts of 10 per cent. formalin and Muller's fluid. The brain, cord and peripheral nerves were then prepared in the usual way. The preliminary fixation is a point of some importance, for handling of the tissues before fixation will give rise to a positive Marchi reaction and in beri-beri, where the changes are slight, this may lead to an error of interpretation. In addition to Marchi preparations of the brain and spinal cord, other brains were stained for Nissl granules by toluidin blue, and others were prepared by the Bielschowsky method.

The peripheral nerves studied were the sciatic and its branches. These were dissected out and fixed on glass slides. Some were stained with silver nitrate, counterstained with safranin and teased in oil of turpentine. Others were

[1] *Biochemical Journal*, vol. xx, 1926, p. 1229.

stained with osmic acid and teased. Others were stained by the Marchi method as already described.

The smaller nerve trunks, the intermuscular portions of the nerves and the nerve endings were stained with methylene blue *intra vitam*, with the Bielschowsky method and with gold chloride. The *intra vitam* staining with methylene blue was especially useful, for by it were obtained excellent preparations of the gut plexus and of the distribution of non-medullated nerves in relation to the capillaries and small vessels in the muscles.

BRAIN AND SPINAL CORD

The Marchi preparations were entirely negative. No trace of degeneration was found in the brain or cord. The silver staining of the brain and cord was followed in serial sections. No changes were found. Particular attention was paid to the paraventricular areas and the hypothalamus because of their supposed association with temperature regulation and functions of the sympathetic nervous system. The cranial nerve nuclei and the issuing nerve roots were also examined with care. No lesions could be discovered. The nuclei of the vagus were quite normal in appearance. The Nissl sections disclosed no chromatolytic changes in the central nervous system. Particular observations were made on the motor nuclei of the ventral horn without revealing any changes in these cells.

These observations lend no support to the hypothesis that the essential lesion of beri-beri is a disorder of lipoid metabolism as shown by the chromatolytic changes in the nerve cells. This was put forward by Findlay (3). His observations were made on birds.

CHANGES IN THE NERVE TRUNKS

The Marchi examination of the sciatic nerve was negative. In a few sections an occasional black dot was observed but these were so rare that a negative interpretation of the results needs no qualification. The teased preparations disclosed normal fibres abundantly. An occasional doubtful fibre could be found but this was extremely rare. However, as the nerves were examined more distally changed fibres were more frequently met with. Here and there the myelin appeared to be aggregated into globular masses leaving the axis cylinder uncovered. The axis cylinder appeared to be always intact despite these changes in the medulla.

Kimura (5) states that it is generally believed that the disease starts peripherally but that this has not been adequately demonstrated. It remains uncertain whether the disease begins in the final termination of the nerve, in the naked axis cylinder, in the smallest intermuscular bundles, or at the entrance to the muscle. Various observers claim to have seen degeneration in the larger nerves, such as the femoral, etc. All are agreed that only a small proportion of the fibres are affected. McCarrison (6) estimates that never more than 15 per cent. of the fibres are involved but that a far greater proportion

have their function impaired. Vedder and Clark (8) estimate that the number of fibres affected is about 10 per cent. They believe beri-beri to be a disease of the whole nervous system. The conclusion that the affection begins in the intermuscular portion of the nerve fibres is supported by the above observations.

THE STATE OF THE NERVE ENDINGS

The beri-beri rats stained with gold chloride (figs. 1 and 2) showed that the changes in the endings were considerable. The normal ending is a fine branching complicated net-like ending of the axis cylinder beneath the sarcolemma of the muscle fibre. In the deficiency disease, the rich complication becomes lost. In some cases the medullated fibre appears to end blindly and to bear no nerve ending at all. In other cases the fibre ends in a bulbous manner, indicating the position of what was once an end organ. More commonly the fibre forms an ending, but this differs from the normal in that the finer branching is no longer visible and the ending is coarse and has lost its delicate tracery. The individual elements are swollen and expanded and give the ending a gross and deformed appearance. The fibre connected with the ending may be much altered, but in general, the alteration in the nerve fibre is much less than that of the ending. In the nerve fibre the change usually takes the form of a swelling of the myelin, which would appear to be more fluid since the nerve fibres become irregular in outline. The changes are most marked where the nerve fibre pursues an intramuscular course, and becomes progressively less marked as the individual fibres are followed back to where they join the nerve bundles. The changes appear to affect first the myelin. Fragmentation of the myelin, the formation of droplets in the myelin and disappearance of the myelin can be observed. The axis cylinder may have disappeared or become fragmented, but as a rule it persists even when the myelin has been much altered. From a study of the gold-chloride preparations it would appear that the changes are most marked in the nerve endings and in the myelin and then in the axis cylinder where it is covered by myelin, and that these changes are best seen in the intermuscular portions of the nerves where they have separated into groups each of a few fibres running towards their own terminal plates.

The silver preparations (figs. 3 and 4) are the least satisfactory for study, and Kimura (5) also records his dissatisfaction with the method. The mode of ending is not demonstrable, for silver preparations have to be studied in sections, whereas the others are spread out so as to permit the examination of the whole fibre, in continuity with its ending. The silver specimens show a similar irregularity in the outline of the nerve fibre, which appears to be swollen and expanded right to its ending. The endings have lost much of their finer branching. The changes are seen best in the intermuscular part of the nerve.

A study of the methylene-blue preparations (fig. 5) shows that in some fibres the axis cylinder may be intact but in others it may be irregular and its ending become a large bulbous swelling. The naked terminal network is

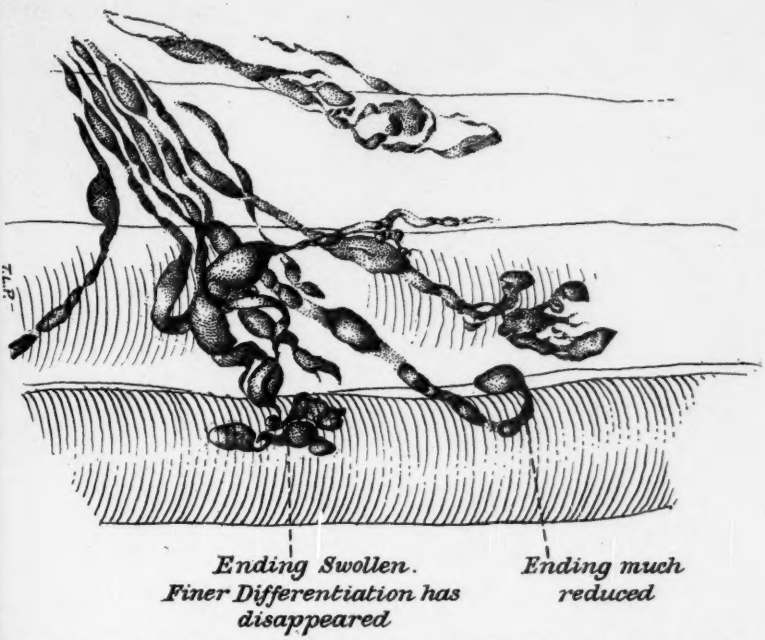

Fig. 1. Terminal motor nerves and endings. Stained with gold chloride. Vastus medialis of rat with severe beri-beri. × 1000. For detailed description see text.

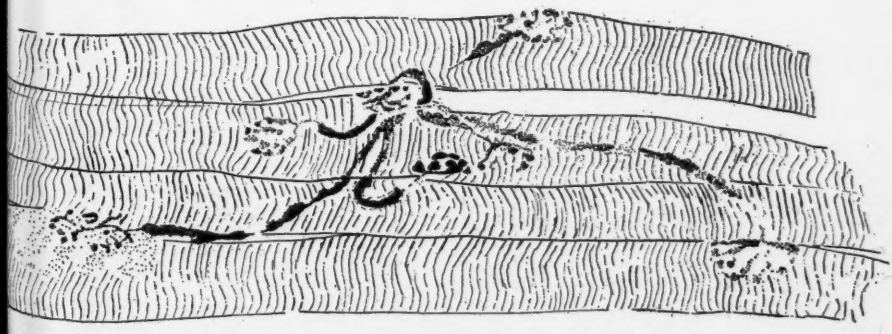

Fig. 2. Terminal motor nerves and endings of the muscles of front of thigh from rat with moderately severe beri-beri. Gold chloride. × 500.

swollen. The normal thickenings in the terminal apparatus have become large bulbous discs. The finer branches have disappeared or perhaps fused to give rise to the larger bulbs that are present. The total size of the ending is reduced, though the few elements present are much swollen. The axis cylinder beyond the terminal apparatus may be affected, but on the whole it is the part of the nerves which has undergone least change. The myelin may have disappeared

Fig. 3. Terminal fibres and endings in the thigh muscle of rat with moderately severe beri-beri. Terminal fibres irregular in outline and the endings confused and reduced. Bielschowsky method. ×500.

Fig. 4. Transverse section of a nerve trunk lying embedded in the muscle. From thigh muscle of a rat with moderately severe beri-beri. The axis cylinders in section are irregular in outline. ×500.

in part or become much expanded. The nerve outline is grossly irregular. The regular succession of the nodes of Ranvier have disappeared. The staining varies considerably and is much less efficient than in the healthy animal. The nerve ending is stained rather palely.

The changes that have been described for the motor terminal plate apply equally well to the muscle spindles (fig. 6). The apparatus in both methylene-blue and gold-chloride methods has lost its definition, many of the individual loops are wanting or they are swollen or confused in outline. The changes are not restricted to the ending but are also apparent in the approaching nerves

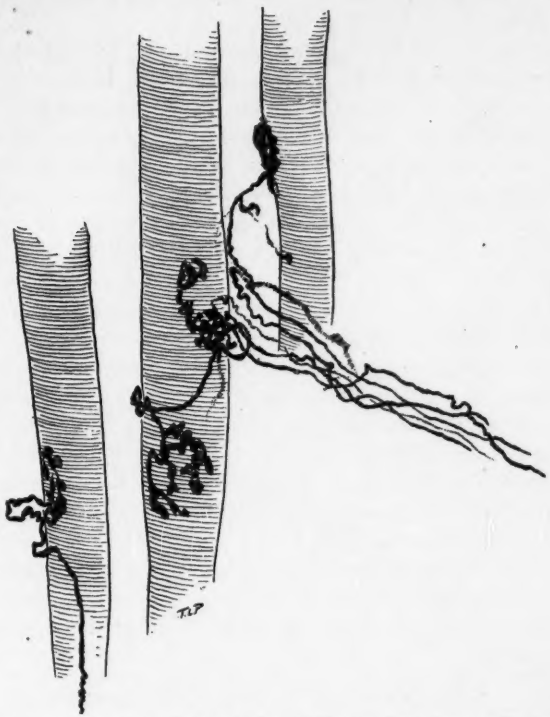

Fig. 5. Thigh muscle of a rat with mild beri-beri. Methylene blue *intra vitam* staining. Slight changes in the nerve endings. ×500.

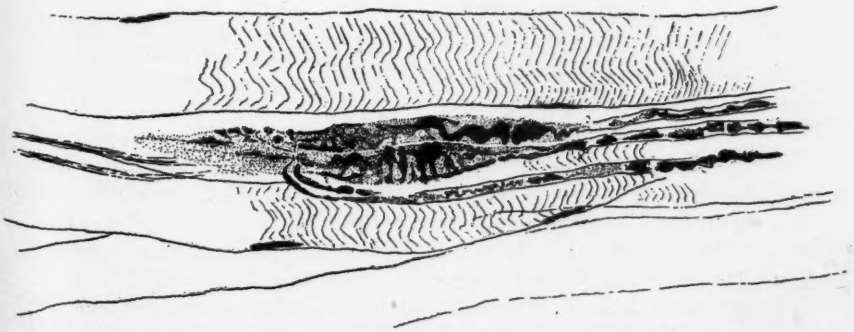

Fig. 6. Neuro-muscular spindle from thigh muscle of rat with severe beri-beri. The morphological details of the end organ have become much obscured and lost. ×500

and these too show changes mainly in the myelin, but also to a varying extent in the axis cylinder.

The observations on the terminal apparatus of the motor and sensory nerves in the muscle may be summed up as follows. In some cases there has been a disappearance of the endings. This is rare. In more cases the endings are swollen and have lost their finer differentiation. Others are only slightly changed or not at all. The myelin appears to have suffered more than the axis cylinders. It appears to have assumed a more fluid consistence, as shown by the irregularity in outline and in the spreading of the sheath from even such slight pressure as the crossing of two nerve fibres. These changes are most pronounced near the ending of the nerve and become less marked as one approaches the larger nerve bundles entering the muscle.

When these observations are compared with those of other observers, it is to be remarked that no paper dealing with the changes in the nerve endings has been found. Some importance should be attached to the state of nerve endings as the neuro-muscular apparatus offers a highly differentiated field in which slight morphological changes might be easily observed. The changes are conspicuous and of varying degree. I believe they offer a better basis than has hitherto been suggested for the quick recovery that occurs when the animal is given the vitamin.

The degree of the changes in the intermuscular portion of the nerve fibres and the nerve endings as compared with the paucity or absence of changes elsewhere suggest that the disease exerts its effects at this point.

THE SYMPATHETIC NERVOUS SYSTEM

It would seem that this system has never been adequately investigated. McCarrison (6) has reported changes in the cell of coeliac ganglion and in Auerbach's plexus. Kimura (5) expresses the opinion that this system must be affected, but apparently made no observations on it.

Coeliac ganglion. In several rats these ganglia were removed and after fixation in alcohol were stained with toluidin blue and the cells investigated. No changes of any sort were found in these cells. The Nissl granules were unchanged and the absence of any sort of chromatolytic changes was beyond doubt.

By means of methylene blue the state of the gut plexus was investigated and here again I was able to find no definite changes in the cells. There seemed to be a considerable reduction in the richness of the nerve fibres of this plexus. There is much atrophy and wasting of the muscle and glandular coat, but nothing definite in the way of affection of the plexuses was ascertained except this reduction in the abundance of nerve fibres.

Voegtlin and Lake (9) fed dogs, cats and rats on alkali-treated meat. The rats never developed beri-beri. Some dogs escaped the disease; others died without nervous symptoms; others developed incoordination, spasticity, and

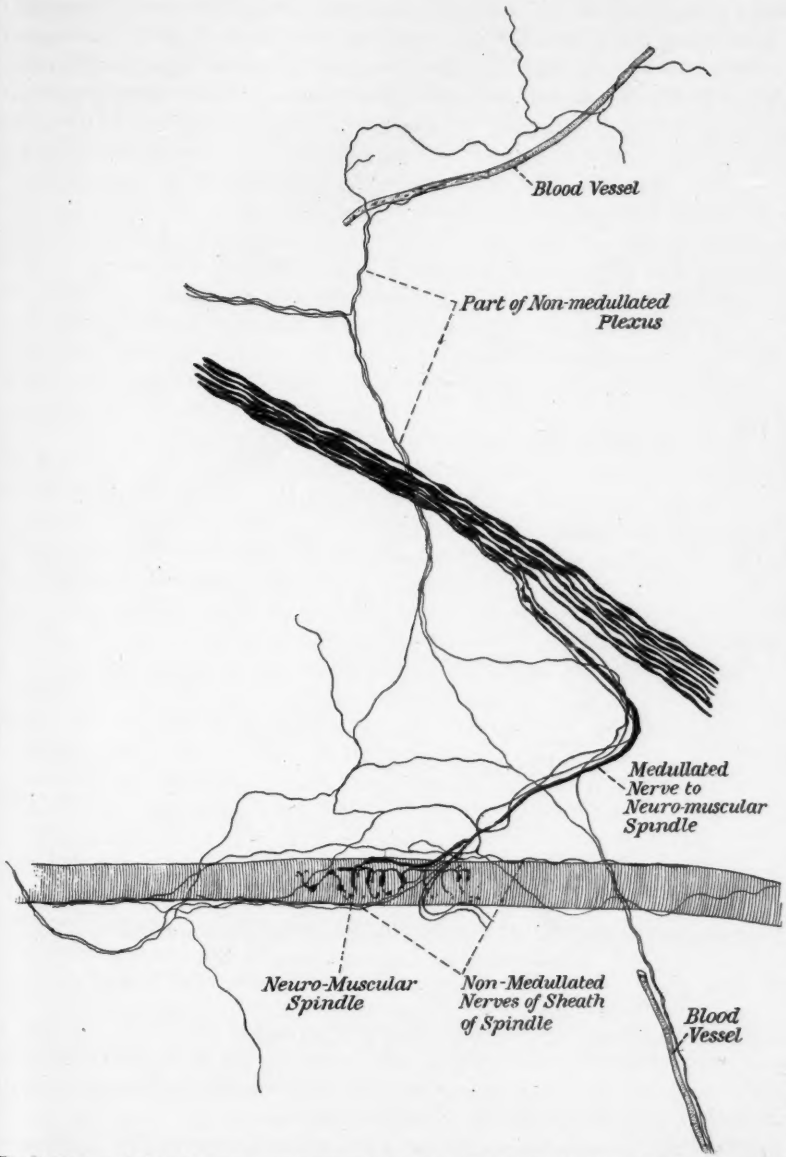

Fig. 7. Non-medullated nerves, neuro-muscular spindle and capillaries from the muscle of the thigh of a rat with severe beri-beri. The non-medullated nerves issue from the nerve trunk. Methylene-blue preparation. For description see text. ×500.

convulsions. Stimulation of the sciatic nerve gave qualitatively normal results, while stimulation of the cervical sympathetic was followed by immediate dilatation of the pupil. Marchi examination disclosed degeneration in the sciatic nerve varying from mild to severe and a scattered degeneration was also present in the cord. There was no correspondence between the degenera-

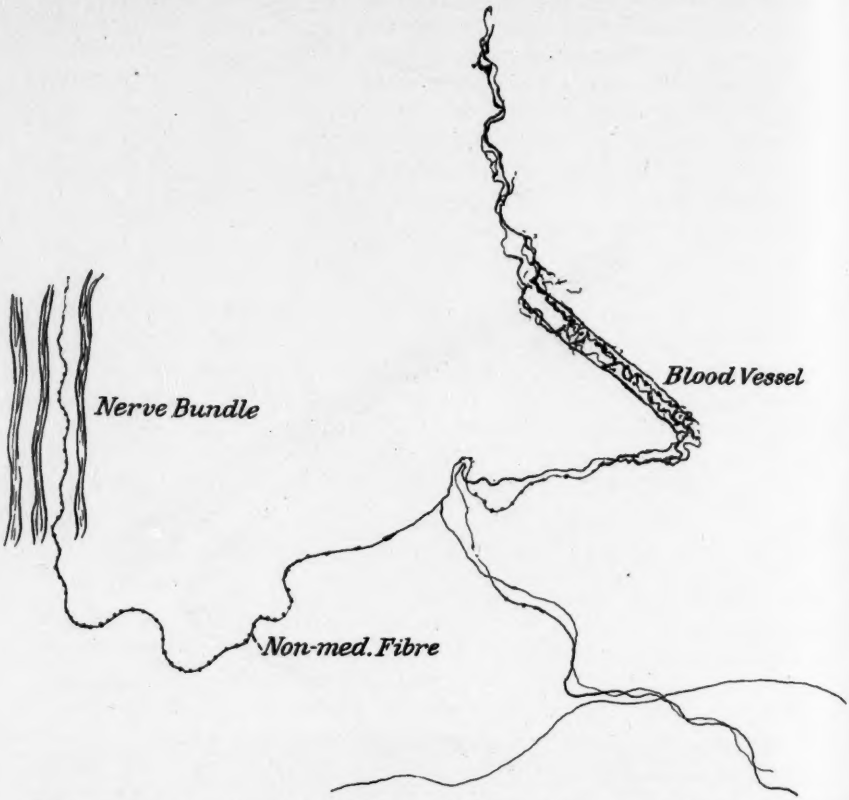

Fig. 8. Similar preparation to fig. 7 showing the distribution of non-medullated fibres from a methylene-blue preparation of a muscle. × 500.

tion and the symptoms observed. Kimura (5) says it is difficult to understand how the peripheral vascular system behaves during life in beri-beri; that it is not normal one can well believe because the sympathetic nervous system must be depressed organically or at least functionally.

The methylene-blue preparations of the muscles of the beri-beri rats were particularly favourable for the study of the distribution of the fibres belonging to the sympathetic system. They were clearly stained and could be followed

for relatively great distances in such preparations. Figs. 7 and 8 are drawn from such and show clearly that there has been no change in the peripheral non-medullated fibres. These form a very considerable plexus in the sheath of the muscle which they reach mainly from the branches which run in the nerves to the muscle. They can be followed in the nerve bundles and often subdivide while still in these bundles. After leaving the nerve bundles they ramify widely and so form a considerable plexus. The distribution of the branches of this plexus often brings them into close relationship with other nerves, and in fig. 7 they are seen in relationship with a neuro-muscular spindle. They appear to wrap themselves about the sheath of the spindle. However, out of the plexus individual fibres can be traced and they come into relationship with blood vessels. On these they can be traced for long distances, gradually growing finer and finer until they pass beyond the range of visibility.

These very clear preparations of the sympathetic fibres can leave no doubt that this system is not involved in the degenerative changes that overtake the endings of the muscle nerve fibres.

A qualitative examination of the adrenals in a great number of cases has been made. In all cases the cortex appeared to be quite normal and there was no deviation from the normal in the fat staining of the cortex. Findlay (3) believes that the enlargement is cortical and correlates this with chromatolytic changes in the nerve cells. In all cases there was an abundance of chromaffin in the medulla of the suprarenal. This has been noted by McCarrison (6) and Kelleway (4). The latter suggested that though there was this abundance of adrenalin, yet it was possible that it might not be discharged into the blood stream because the normal outlet into the medullary sinuses appeared to be obstructed by an accumulation of cells belonging to the cortex. A study of the serial sections of the glands does not confirm this view of Kelleway. The disposition of the medullary substance shows no deviation from the normal and there is no reason why the normal method of discharge should not operate; at any rate this obstruction by cortical cells is not present when serial sections are examined.

From this study of the nervous system, it is concluded that the changes in this system begin in the terminations of the nerves in the muscle, that the change spreads back into the nerve bundles in the muscle and grows less the farther the nerves are followed. In the larger trunks it is difficult to find any fibres affected. The sympathetic system escapes entirely, and at the same time there is an abundance of chromaffin substance in the suprarenal with the same disposition in regard to the veins of the medulla as in the normal animal.

CHANGES IN INANITION

It is obvious that the findings in the beri-beri animal present a close parallel with the changes that occur in an animal that is deprived of all food. Wasting, muscular asthenia, hypothermia, hypertrophy of the suprarenal are common

to both (McCarrison). It is true that, save for Eijkman, observers are accustomed to confirm the idea that the polyneuritis is peculiar to beri-beri. It is to be remarked that many animals die without showing any nervous manifestations; that on the same diet many animals do not develop the clinical picture of beri-beri; that in all cases (pigeons, dogs, cats, rats) the symptoms, when they are present, disappear in a few hours, six to twelve, after the administration of the appropriate vitamin. The experimental cases are not comparable to what occurs in the chronic cases in man, as presumably there the time allows of far-reaching degeneration of the nerves.

In view of these facts it became important to determine whether the same picture occurred in animals deprived of all food.

The same methods were used as in the case of beri-beri. Preparations of the terminations of nerves in the muscle were made by the various methods and an examination of figs. 9 and 10 will show that real changes do occur in the nerves and at the same place as happens in beri-beri. The changes are decided, but they are not so pronounced as in beri-beri. Many normal endings are present. They are, of course, present in beri-beri, but more fibres are there affected. The changes are of the same kind. The arborisation of the terminal motor plate becomes reduced and the finer elements are no longer seen, or the ending becomes bulbous and confused. The changes extend into the nerve-bundles of the muscle, and an occasional altered nerve fibre can be found in the nerve trunk. The changes in animals deprived of food are of the same kind and distribution as occurs in the beri-beri animal. They are not so extensive and are more strictly localised than in beri-beri. The rats were deprived of food for four to six days. A rat on a deficient diet takes about three to four weeks to reach the same condition. This difference in duration may be a sufficient explanation for the differences that occur in the condition of the peripheral nerves in the two cases. In the animals allowed to nibble yeast extract at will, though deprived of food, changes in the terminal motor apparatus have been observed, but it is very difficult to establish differences between these and the former group. I believe that the changes are slighter in the terminal apparatus of the nerves in this series than in the series receiving no marmite.

It is not my purpose to discuss the various theories of beri-beri. This much might be said, that many of the nervous symptoms occurring in animals during acute feeding experiments for the production of beri-beri cannot be confirmed. A clinical examination of a rat suffering from beri-beri is not easy, but some observations can be made. They can be tested for righting reflexes and these they respond to as does the normal animal. They are not spastic. From the nerve lesions present it is difficult to understand why spasticity should be so frequent in the description of beri-beri. Convulsions, as a final event in the disease, permit of many explanations. Occurring in the course of the disease what I have seen described as such is an alternate flexion and extension of the hind extremities in the rat without any general manifestations.

Fig. 9. Gold-chloride preparation of motor nerves and terminations from a rat that had been deprived of food for five days. ×500. Note the changes that have occurred in some of the nerve endings.

This lasts only for a brief time and may not occur again in the course of the disease. The extraordinarily rapid cure of beri-beri, which admits of no doubt, is inconsistent with any profound change in the nervous system. Moreover, it is consistent with the changes here described which are partially restricted in their distribution and confined mainly to the terminal apparatus of the

Fig. 10. Teased preparation of tibial nerve in the leg. From a rat deprived of food for five days. Osmic-acid stain. The axis cylinders intact. Alteration in the myelin.

nerve fibre. Absolute destruction is uncommon. More frequently the changes are of such a nature as would permit of imperfect function and certainly of quick recovery.

How far are they consistent with the idea that beri-beri is a disease due to the absence of a vitamin which causes the animal on such a diet to be progressively more unable to assimilate the food offered so that it gradually passes from a state of semi-starvation to complete starvation?

The agreement between the two conditions is extraordinarily close. The cardinal symptoms are the same; the wasting, the hypothermia, the hypertrophy of the suprarenal, the atrophic change of other organs and the alteration in the structure of the terminal apparatus of the nerve fibres in the muscle. The more decided nervous manifestations of beri-beri might be explained by the different duration of the two conditions. If this were so one might with some confidence put forward the notion that beri-beri as it occurs in rats under experimental conditions is really starvation arising from the inability to assimilate food in the absence of the appropriate vitamin. No observer has proclaimed that the pathological findings can be correlated with the symptoms observed during life. Kimura (5) definitely finds that head retraction in the pigeon is an early phenomenon, while affection of the cervical nerves is a very late phenomenon.

SUMMARY

(1) The morbid changes in the nervous system of the rat on a diet deficient in water soluble vitamin B affect the intermuscular medullated motor and sensory nerves and their endings. The changes rapidly subside as the nerves are examined further away from the muscles.

(2) The sympathetic nervous system presents no abnormal anatomical change.

(3) The central nervous system presents no abnormal anatomical change.

(4) Rats, deprived of food, show the same type and distribution of lesions as the rat on the deficient diet. They are not, however, quite so marked.

(5) Both series, deficient diet and no diet, show qualitatively an abundance of chromaffin substance.

(6) There is no histological evidence that the cortex of the suprarenal is affected.

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A NOTE ON THE INTRACRANIAL AND EXTRACRANIAL PARTS OF THE IXTH, XTH AND XITH NERVES

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It is obvious that the size of a nerve trunk is not necessarily an index of the number of nerve fibres which it contains. Among the factors which influence the size and even the form of a nerve trunk are the mechanical conditions to which it is subject during life. If such a nerve as the external cutaneous of the thigh be carefully examined it will be found to vary in size and form. Sections of the nerve where it is surrounded by the substance of the psoas muscle, as it is contained in the fascia occupying the iliac fossa and as it lies embedded in the fascia lata of the thigh, present a great contrast to one another. When the surrounding tissue is less resistant the nerve trunk is rounded or oval; on the other hand, when this tissue is more resistant the nerve trunk is flattened and ribbon-like.

Variations in size of nerve trunks, which are obviously due to the mechanical conditions to which they are subject, are perhaps most manifest in the extracranial and intracranial portions of the cranial nerves. This is particularly the case as concerns the spinal accessory, vagus and glosso-pharyngeal nerves, which are relatively small trunks within the cranial cavity but are conspicuously larger below the jugular foramen.

In order to investigate the actual condition of these nerve trunks in the intracranial and extracranial parts of their course, sections were made of nerves taken from a child three months old and others from an adult. The sections taken from the three-months-old child were not completely satisfactory as the subject was not a fresh one, but the sections from the adult (specimen obtained from the post-mortem room and placed immediately in formalin 5 per cent.) were in very good condition. These sections were stained by the following methods:

(1) Iron haematoxylin, counterstained with eosin and 10 per cent. Mallory solutions.

(2) Orange fuchsin.

(3) Picro indigo carmine.

(4) Van Gieson's solution.

Further sections were made from similar specimens removed from another adult human subject and were stained with osmic acid.

On examination, the most obvious difference was the relative amount of the supporting tissue. The intracranial part of each nerve was surrounded by a thin loose sheath, while the tissue intervening between the funiculi was exceedingly scanty (figs. 1 and 2). On the other hand, the extracranial parts of the nerve were surrounded by a very thick dense sheath of epineurium; the perineurium was also relatively thick and dense, but there was no very obvious difference in the endoneurium or the tissue surrounding the individual fibres in the two cases (figs. 3 and 4).

Numerous large blood vessels (vasa nervorum) with well-marked fibrous sheaths were a conspicuous feature in the epineurium of the extracranial nerve trunks, while in the sheath surrounding the nerve trunk within the cranium, blood vessels were scanty and small. The intraneural vessels contained in the extracranial nerve were numerous and were especially large and noticeable in the spinal accessory. The difference in size of the intracranial and extracranial parts of these nerves are, therefore, mainly due to the relative amounts of the supporting and vascular tissues.

An attempt was made to estimate the relative amount of myelin in the individual nerve fibres of the intracranial parts of the nerves as compared with the extracranial parts. For this purpose the spinal accessory nerve was selected, as the vagus, owing to the very varied size of the fibres of which this nerve is composed, was unsuitable. The spinal accessory is composed of relatively large and relatively small fibres, the fibres of intermediate size not being conspicuous. On comparing the larger fibres in the two parts of this nerve, I came to the conclusion that the fibres were relatively larger extracranially than intracranially, and that this was due to a relative greater thickness of the myelin sheaths. No actual measurements were made, and this point requires further investigation.

One remarkable feature presented by the extracranial trunks of the vagus and glosso-pharyngeal when they are sectionised at a point considerably distal to their ganglia is the presence of nerve cells. These cells were conspicuous in the nerve trunk of the vagus where they consisted of large ganglion cells surrounded by a sheath containing flattened nuclei, the nuclear membrane was surrounded by a clear zone of hyalo-plasm and the cell body was faintly granular (fig. 5). In tracing these cells through several sections they appear to be bipolar, the long axis of the cell corresponding to that of the nerve fibre. These cells appear singly or in groups: they were present in the extracranial portions of all the three nerves examined. The largest group of these ganglion cells was found, however, in the spinal accessory nerve; many of them appearing close together in one section (fig. 6). No ganglion cells were found in connection with the intracranial trunks of the nerves. As the nerve cells were more abundant and conspicuous in the nerves from the three-months-old child than in the nerves of the adult, it is probable that, as far as the vagus and glosso-pharyngeal are concerned, the nerve cells undergo distal migration in the course of growth. Nerve cells in the trunks of the glosso-

pharyngeal and vagus distal to their ganglia are a well-known feature of these nerves, and have been described by Barratt, Streeter and others.

The extracranial part of the spinal accessory examined was in all cases the more distal part of that portion of the nerve which extends between the jugular foramen and the point of entry into the sterno-mastoid. The group of nerve cells found in this part of the nerve were apparently confined to one funiculus only. No nerve cells were found in the corresponding part of this nerve in the adult. It is possible that the condition found was anomalous. Evidence in favour of this possibility was afforded by a 7th-month foetus, in which the whole length of the nerve between the ganglion nodosum and the point of entry into the sterno-mastoid was most carefully examined and no trace of a nerve cell could be found. That nerve cells should appear in association with the spinal part of the spinal accessory is not a matter for surprise. Developmentally, the nerve contains both motor and sensory elements, and its extracranial trunk must contain afferent (proprioceptive) fibres from the trapezius and sterno-mastoid. Streeter (4) has shown that when the fibres of the spinal accessory first appear they are enclosed by the cells of the caudal prolongation of the ganglion crest, the most oral part of which gives rise to the ganglion of the root (jugular ganglion) of the vagus. The ganglion crest is at first continuous, but subsequently becomes subdivided into clumps of nerve cells which persist and, as is well known, may be found in the adult on the rootlets, both medullary and spinal, of the spinal accessory. It is conceivable that these cells have a tendency to distal migration which may take place to such extent as to appear in the extracranial part of the nerve.

I have to express my thanks to Professor Barclay-Smith for the suggestion of making this investigation, to Dr Gladstone for his very valuable help and his artistic skill in drawing some of the figures, and also to Dr H. A. Dunlop for supplying the adult specimens and helpful criticism.

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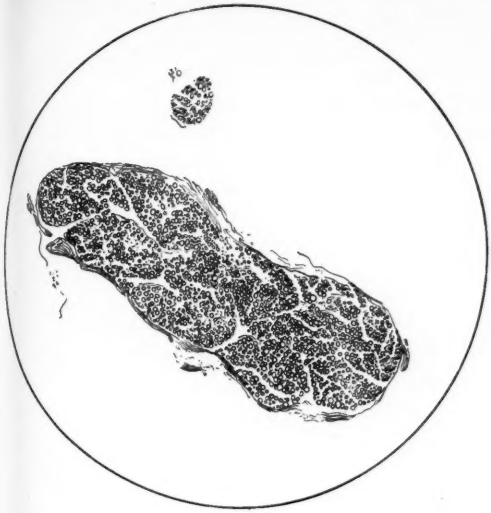


Fig. 1.

Fig. 2.

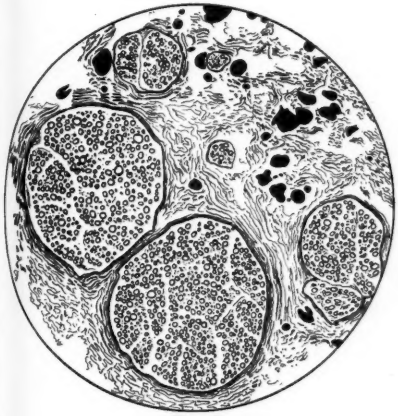
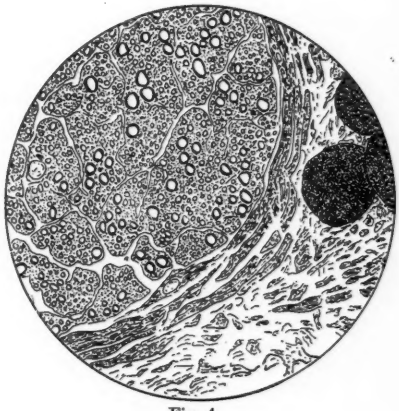


Fig. 3.



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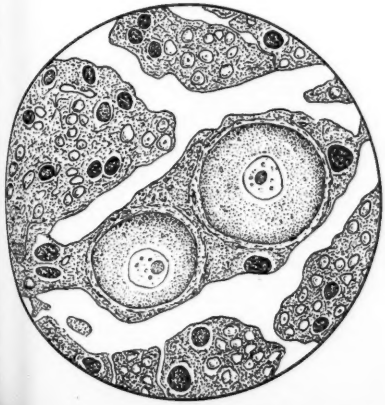

Fig. 5.

Fig. 6.

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DESCRIPTION OF PLATE

Fig. 1. Intracranial part of spinal accessory from adult, stained in osmic. Ob. $\frac{1}{2}$ in. Oc. × 3.

Fig. 2. Intracranial part of vagus nerve, stained in osmic, from adult. Ob. $\frac{1}{2}$ in. Oc. × 3.

Fig. 3. Extracranial (spinal) part of spinal accessory from adult, stained in osmic. Ob. $\frac{1}{2}$ in. Oc. × 3. The wide separation of the funiculi and the abundant tissue containing fat cells are very conspicuous.

Fig. 4. Transverse section through part of a funiculus of the extracranial portion of the vagus nerve, from an adult human subject. The section shows the thick outer covering of epineurium, containing three fat cells, and a dense layer of perineurium surrounding the funiculus. The large medullated and small medullated nerve fibres are distinctly brought out by the osmic acid staining.

Fig. 5. Transverse section of vagus nerve below the ganglion of the trunk, showing ganglion cells, from a child three months old. × 750 D.

Fig. 6. Section through a funiculus of the spinal accessory nerve, below its communication with the vagus and about half-an-inch from the point where it entered the sterno-mastoid muscle, showing a group of ganglion cells. From a child three months old. Ob. $\frac{1}{6}$ in. Oc. × 2.

The figures 1 to 6 have all been reduced by half.

OBSERVATIONS ON THE DEVELOPMENT OF THE HUMAN SUPRARENAL GLAND

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The study of the changes that occur in the minute structure of an organ during its development naturally arouses curiosity as to the nature of any concomitant acquisition of function or changes of function which may occur, and though the main object of this paper is to describe the minute structure of the developing human suprarenal gland as fully and as consecutively as the material at our disposal allows, the scope of the investigation also includes the determination of the earliest appearance of adrenin, the general distribution of lipoid, and the variations that occur in certain cases of abnormal development.

The possible function of those cells constituting the main mass of the human gland during development (the so-called foetal cortex or boundary zone(1)) which disappear during the first year of life offers a most interesting problem, but the very fact that these cells are present mainly during foetal life puts great and very obvious difficulties in the way of any investigation of their physiological significance. We have given considerable attention to the question of the part played by the foetal cortex, but as yet we are unable to offer any definite evidence on this point.

We feel that a solution of this problem may be found in the study of the comparative anatomy and physiology of the foetal ductless glands, but at present the scope of our investigations cannot be further extended.

The evidence presented in this paper is based on our own dissections and observations of some 300 embryos and foetuses ranging from one of 5 mm. to full time. Examination of isolated organs was made also of post-natal material (30 cases) ranging from birth to 3 years. Serial sections were made of some of the earlier embryos comprising one 5 mm., one 10 mm., two 12 mm.[1], one 18 mm., one 25 mm. and several 30–40 mm. embryos, and also of glands at various later stages of development.

Owing to the small number of young human embryos amongst our specimens the early development could not be followed very systematically, but

[1] One of the 12 mm. embryos was measured after fixation and probably represents a slightly later stage of development. The other 12 mm. specimen was somewhat damaged, and is not described.

from the 8th week of foetal life to the time when the gland attains its adult characteristics the development of the suprarenal has been followed in detail.

The age in weeks of specimens measuring more than 40 mm. (vertex rump) was computed by taking into consideration all factors bearing on maturity, menstrual history (not always available), length (vertex-rump and vertex-heel measurements), weights, ossifications, appearances of hair and subcutaneous fat, general appearances, etc.; and a graph is appended for reference (diagram 1) showing the relation between vertex-rump measurement and the age in weeks of our material.

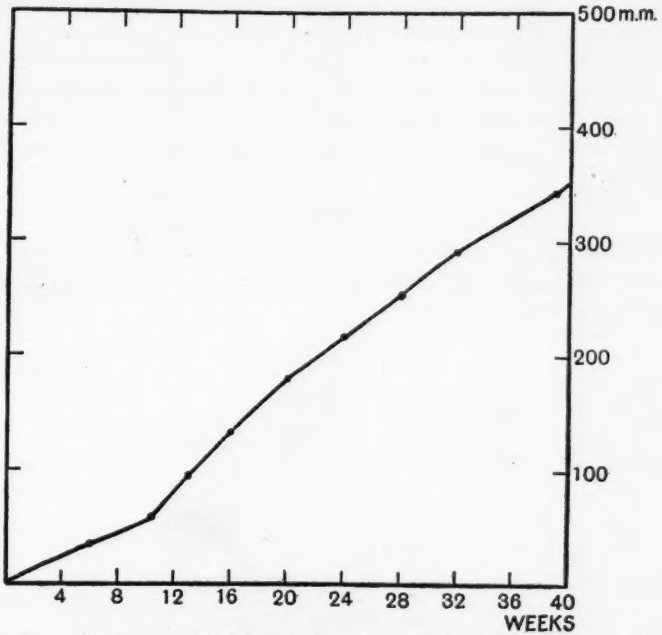

Diagram 1. Curve showing the relationship of the vertex-rump length of the foetus to the age in weeks.

The following table shows briefly the relationship of the vertex-rump length of the foetus to the age in weeks:

Average vertex-rump length in mm.	Maturity in weeks	Number of cases
33	5–6	3
57	10–11	5
98·5	12–14	3
136·5	16	10
178	20	16
215	24	8
252	28	5
284	32	9
340	About full time	50

GENERAL APPEARANCE

Specimens up to the age of 8 weeks (30–40 mm.) were all cut in serial section without dissection in order that the relations to the surrounding structures might be preserved, and consequently until these have been reconstructed no observations as to size and shape are available; but already at 6 weeks the gland is a clearly defined organ situated on the upper pole of the kidney, and by 8 weeks its maximum cross-section equals that of the kidney. It maintains its relation to the kidney throughout development, its surface at first being smooth, the characteristic fold only appearing after the sixth month of intra-uterine life.

A fresh full time gland when cut open shows a dark central part surrounded by a thin yellowish rim. The central part is largely composed of blood, the organ being extremely vascular at this time.

After birth the gland obviously shrinks, especially in its antero-posterior dimension.

WEIGHT

The gland shows a steady increase in weight throughout foetal life, and the following figures give the approximate average weight of the gland in successive months (2):

Weeks	Gm.	Cases
16–20	0·5	2
21–24	1·0	4
25–28	1·7	11
29–32	2·2	13
33–39	3·0	9
Full time	Right, 4·47 Left, 4·64	65

Full time. Weight ratio: Right, 762
Left, 642

MICROSCOPIC STRUCTURE

5 mm. Embryo (Diagram 1 *a*).

In a 5 mm. embryo a transverse section cut just below the level of the bifurcation of the lung diverticulum shows bilateral coelomic recesses behind the heart. The superficial or lining cells of the posterior wall of these recesses (taken to be pleuro-peritoneal canals) are of a high columnar type, and form the epithelium of the extreme cephalic end of the Wolffian ridges. Since the embryo was not cut absolutely horizontally the right side of the section shows a slightly lower level, and here two ridges are seen, both covered by the high columnar epithelium. This columnar epithelium is supported by bilateral masses of cells very slightly differentiated from the mesenchyme stretching forwards to the gut from the aortae.

A large vein lies posterior to the lateral part of the ridge which is occupied in lower sections by the mesonephric tubules. Neither in this embryo nor in

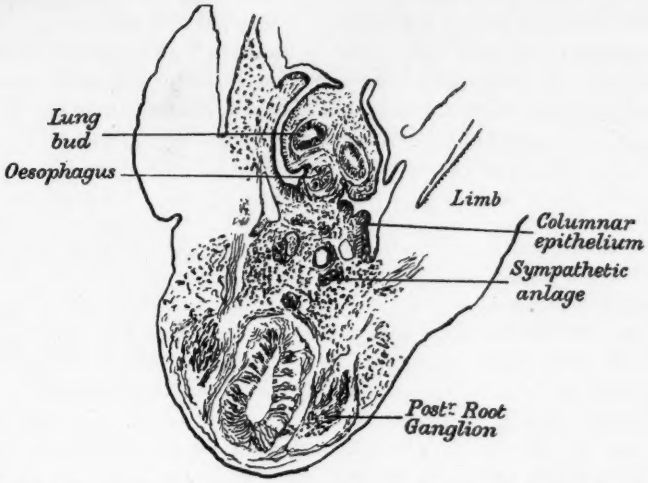

Diagram 1 *a*. Horizontal section through a 5 mm. human embryo just below the bifurcation of the lung diverticulum.

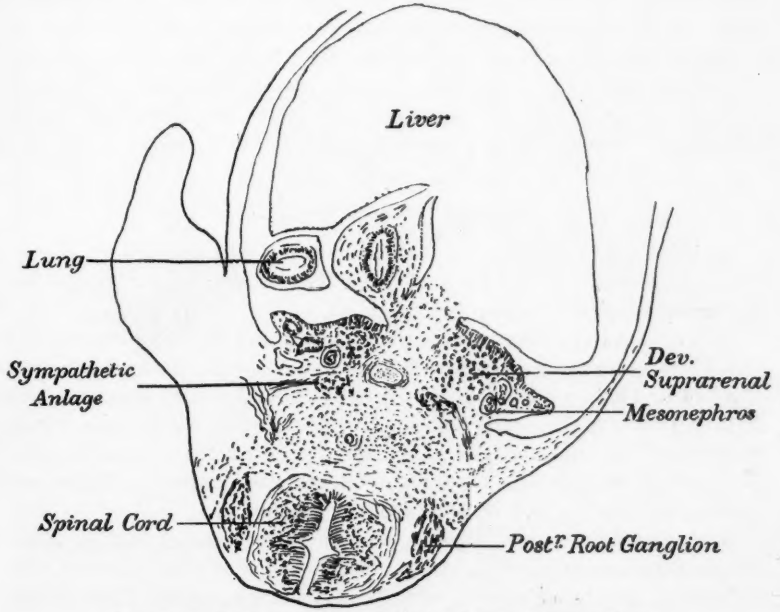

Diagram 2. Horizontal section through a 10 mm. human embryo.

the next (10 mm.) did we see the anlage of the organ in the form of cell buds projecting from the root of the mesentery, as is usually described.

The anlage of the sympathetic system from which is developed the medulla, the third element entering into the formation of the suprarenal, is represented by bilateral masses of rather darkly staining cells situated lateral to the aortae on the anterior aspect of the developing vertebra.

10 mm. Embryo (diagram 2).

Unfortunately this embryo is also cut obliquely, the left side of the section representing a higher level than the right side. On the left side is seen the lower part of the left lung; the section also shows the liver, stomach, root of mesentery, and lateral to the root of the dorsal mesogastrium are the Wolffian ridges. Bilateral masses of cells are seen situated medially to the mesonephric bodies, lying in front of the aorta and having a small free surface covered by coelomic epithelium. These masses of cells are the anlage of the foetal suprarenal, and can be readily distinguished from the surrounding tissues. The nuclei of the cells are large, usually round, vesicular, and show at least one well-marked nucleolus; the cell outlines are not easily made out, but the protoplasm is granular and the cells closely packed together. In contrast, the surrounding tissue shows loosely packed cells of smaller size with small nuclei of varying shape, the structure being that of embryonic connective tissue. The covering coelomic epithelium is of the same high columnar type as that covering the rest of the Wolffian ridge: but at this point the cells are very closely packed together, and show an occasional mitosis.

Immediately behind the bilateral masses are the sympathetic chains, consisting of cells with deeply staining nuclei, and nerve fibres are also seen.

12 mm. Embryo (diagram 3).

In this embryo definite suprarenal bodies are seen situated on either side of the aorta and pushing forwards into the coelomic cavity medial to the mesonephros and developing genital gland.

The cells of the coelomic epithelium immediately on either side of the root of the mesentery are no longer columnar and are proliferating, forming a cap of cells 3 or 4 layers thick over the developing gland (better seen in an 18 mm. embryo); some of these cells tend to push postero-laterally between the mesonephros and the suprarenal mass. Posteriorly this latter is becoming marked off from the surrounding tissues by a developing connective tissue capsule and the cells are big and becoming faintly eosinophil.

On the medial aspect of the gland migrating masses derived from the sympathetic are well seen, and form small groups of cells in the root of the mesentery, closely associated with the large blood vessels. These migrating bundles will be termed sympatho-chromaphil cells (3, 4) from now onwards, and a few are already invading the organ.

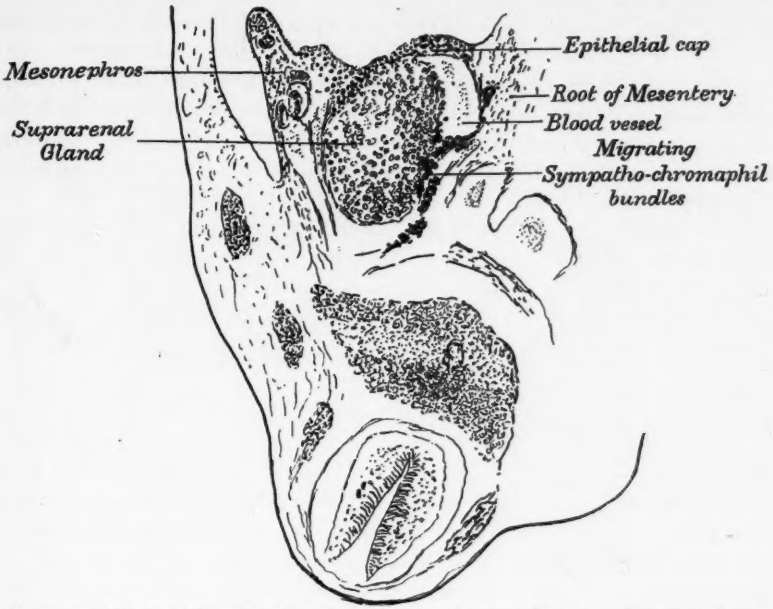

Diagram 3. Horizontal section through the suprarenal region of a 12 mm. human embryo.

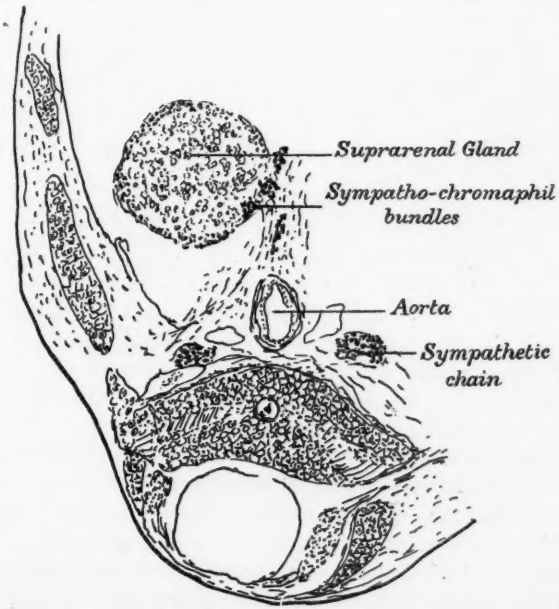

Diagram 4. Horizontal section through the suprarenal region of a 25 mm. human embryo.

25 mm. Embryo (diagram 4).

This embryo exhibits definite paired suprarenal glands. The bulk of the gland consists of foetal cortex or "Boundary zone(1)" cells which are large, irregularly shaped and markedly eosinophil, with large nuclei and well-staining nucleoli. These cells are loosely arranged and the whole mass is very vascular.

The periphery of the gland consists of a thin layer of much smaller cells with darkly staining nuclei: these form the true cortex, namely, that part which will give rise to the entire post-natal cortex.

The migrating sympatho-chromaphil masses are seen in the root of the mesentery, and some bundles have already penetrated well into the gland.

30–40 mm. Embryos.

In embryos of 30–40 mm., that is to say about 8 weeks, the suprarenal glands may be easily recognised with the naked eye. They are seen resting on the upper poles of the kidneys and the two organs are of approximately the same size. The general arrangement of the cells remains unchanged and the whole gland is very vascular, both small and large vessels having extremely thin walls. By now there is a well-marked connective tissue capsule from which delicate strands run into the organ.

The sympatho-chromaphil element is represented by bilateral masses of cells similar to those seen in the sympathetic chains, situated between the aorta and the suprarenal gland. Numerous bundles breaking off from these masses invade the glands chiefly on their medial aspects, and penetrate well into their substance. The cells pass in, in bundles surrounded by connective tissue, penetrating the capsule of the gland where they enter. In addition to this main invasion, bundles of cells pass in with the blood vessels and also penetrate the gland on its lateral aspect.

The invading masses break up to a certain extent after entering and processions of sympatho-chromaphil cells are seen as well as small bundles. Two types of these cells are now recognised, and accompanying nerve fibres are also sometimes seen. The most numerous of the two types of cell are small with a darkly staining nucleus and very little protoplasm; possibly these are neuroblasts because they are frequently found with nerve fibres, and, further, certain of the invading bundles consist of this type of cell only, arranged round nerve fibres and presenting a rosette appearance in section (diagrams 5 and 6). This rosette appearance is that seen in sections of neuroblastomata and affords additional evidence that this type of tumour is derived from embryonic suprarenal medullary cells (5). The appearances were precisely similar to those given in the excellent microphotographs accompanying Wright's description (17).

The second type of cell is larger than the neuroblast and has a vesicular nucleus but is considerably smaller than the cells of the foetal cortex, and

further differs from these in having a basophil protoplasm. These are the so-called "para-sympathetic cells" described by Zuckerkandl (9) but which he did not observe migrating into the gland. Both types of cell persist throughout foetal life, and are the precursors of cells (other than large ganglion cells) found in the post-natal medulla.

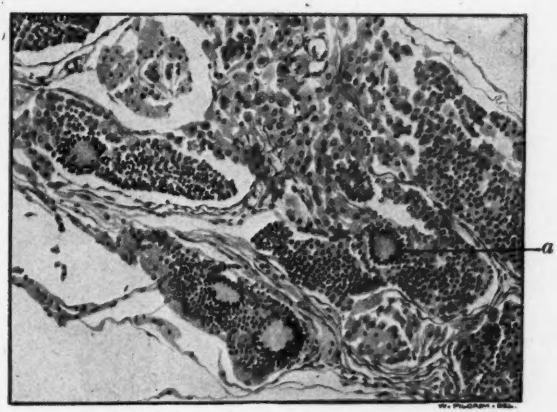

Diagram 5. Human foetus 18 weeks (V.R. 151 mm.). Section of peri-adrenal tissue showing rosette arrangement of cells.

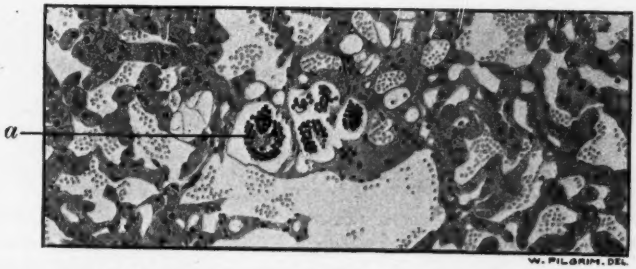

Diagram 6. Human foetal suprarenal 23 weeks (V.R. 225 mm.). Section showing rosette arrangement of invading cells within the gland.

10 Weeks to Full Time.

During the next few weeks of development (10–20) the most striking change occurs in the true cortex. The cells of this layer increase in number (mitoses are seen in an 11-week embryo) and are frequently arranged around a central space. This appearance is especially noticeable in 16-*week* embryos (diagram 7) and the "vesicles" sometimes contain a basophil substance that looks like a coagulated fluid. The vesicular arrangement of the outer zone becomes less

marked during the later months of foetal life, but is present occasionally even after birth. The bulk of the gland still consists of the large eosinophil cells ("foetal cortex") which are arranged quite irregularly and are well supplied with capillaries. Often at this time these cells show many vacuoles, but these are not due to the presence of lipoid which normally does not appear until later. A horizontal section cut through the organ at the hilum shows

Diagram 7. Section through suprarenal of human foetus of 16 weeks (136·5 mm.). *a*, Vesicular arrangement of cells of zona glomerulosa.

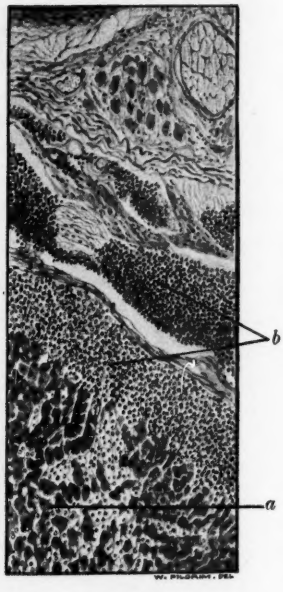

Diagram 8. Section through suprarenal region of human embryo of 12 weeks (v.r. 98·5 mm.) showing infiltration by large numbers of cells from adjacent tissue. *a*, Suprarenal. *b*, Invading cells.

that the central part is occupied by large thin-walled spaces filled with blood round which the penetrating bundles are collecting. In a 12-*week* embryo the immigration was very active, the invading masses consisting for the greater part of the larger cells (diagram 8). This infiltration by cells of the larger type was very marked in this one case only.

No further change is noticed until about the 22*nd week*, when a well-marked chromaphil reaction (3) is given by the larger of the immigrating cells,

situated both inside and outside the gland, and the nuclei of some of these cells show in addition the typical chromaphil ring reaction.

Throughout the *last* 10 *weeks* of foetal life the true cortex increases gradually in thickness, although the foetal cortex constitutes the bulk of the organ until birth. The foetal cortex shows a tendency to congestion, and haemorrhage associated with a progressive degenerative change occurring chiefly in the cells of the deeper layers, the cell boundaries becoming very indefinite and the nuclei acidophil or non-staining. The sections show in addition an increase in the fibrous tissue around the central blood vessels; this is seen by the 26th week and is well marked by the 32nd week.

From the 22*nd to the* 32*nd week* the immigration of cells is still well marked, the penetrating bundles consisting at that time almost entirely of the larger type of cell. Nucleated cells, apparently erythroblasts, are frequently seen in capillaries and large sinuses from the 22nd week until full time. It is difficult to account for their presence in such numbers in the suprarenal at this time since already by the 12th week the blood in the heart shows very few erythroblasts.

The Suprarenal at full time

At full time the suprarenal still consists chiefly of the true and the foetal cortex, but a very thin central zone of medullary cells is seen surrounding large blood sinuses. The outer rim of small polygonal healthy cells, now much thicker, is invading and replacing the inner degenerating foetal cortex (diagram 9). This outer rim gives rise after birth to the whole of the true cortex, and already shows a well-marked zona glomerulosa and beginning zona fasciculata. The immigration of cells through the cortex is ceasing.

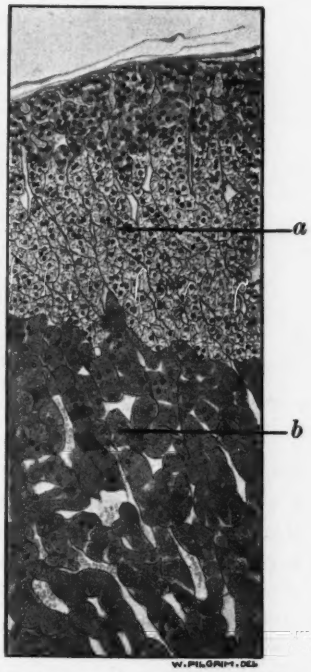

Diagram 9. Section through full-time human suprarenal. *a*, True cortex cells growing in to replace foetal cortex. *b*, Foetal cortex cells degenerating.

The medulla consists of the two types of cells previously described: (1) small round cells with darkly staining nuclei, the original undifferentiated immigrating cell, (2) larger and somewhat irregularly shaped cells of varying size that give a well-marked chromaphil reaction.

In serial sections of the full-time foetal gland the medulla is seen to form a central core which links together the blood sinuses near the hilum, and is spread out in a very thin layer around many of these vessels, and stretches a

short distance into the peripheral part of the organ. The cells are arranged in irregularly sized clumps containing both types, the larger predominating. In addition, ganglion cells are sometimes seen together with nerve fibres close to the hilum.

The Beilschowsky method of staining shows that the gland at full time is very richly supplied with fibres that stain black by this method. No doubt many of these are nerve fibres, but probably many are collagen (Da Fano); this is borne out by the Mallory method of staining. Hammar (18), making use of this method, states that the gland in the foetus of 16 mm. is already richly innervated.

Changes during the first year

The whole gland shrinks owing to the rapid disappearance of the foetal cortex, the cells of which first become swollen, and then lose their nuclei, and

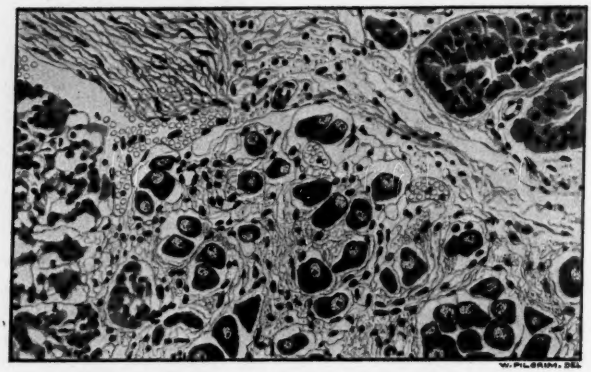

Diagram 10. Section through suprarenal of a child aged 3 months, showing ganglion cells.

are later replaced to a certain extent by temporary fibrous tissue which forms a well-marked zone central to the rapidly developing zona fasciculata. In this fibrous tissue are to be found large isolated eosinophil cells, possibly a degenerative stage of cells of the foetal cortex, and here also basophil granular masses are frequently seen. Up to one year the central fibrous tissue is a marked feature, but can no longer be discerned at three years of age.

The chief change in the true cortex during the first year is the growth of the zona fasciculata, the cell columns being definitely grouped by the third week, and the zona reticulata being defined by 3½ months. It is to be noted that this newly-formed cortex is not nearly so vascular as the foetal structure.

The medulla appears as scattered masses of cells situated principally in the region of the hilum and surrounding the blood sinuses. The thin peripheral portions of the gland show only cortex and the fibrous layer with some central blood vessels. The medullary cells are of irregular shape and of varying sizes,

with darkly staining nucleus and a basophil cytoplasm. The cell boundaries are very indistinct. Nerve fibres are seen between the cells, and ganglion cells are met with in the region of the hilum and sometimes invade the gland (diagram 10). The chromaphil reaction is as a rule not well marked, but as the number of specimens examined was small and removed from infants who had died of various diseases this may not be the normal condition.

Lipoid[1] (diagrams 11–16).

The distribution of lipoid has been investigated by means of the formalin fixation and Sudan III staining method only, and no attempt has been made to distinguish between the different fatty substances present (6, 16).

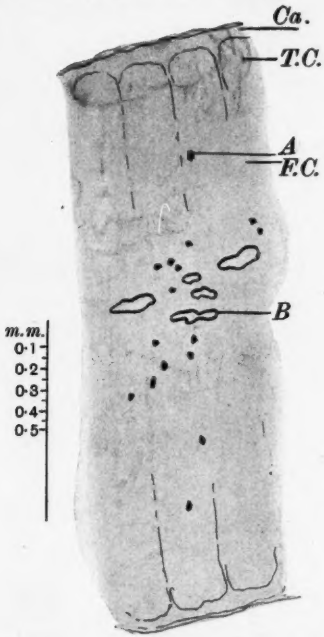

Diagram 11. Human foetal suprarenal 16 weeks (v.r. 136·5 mm.). Section stained for lipoid. *Ca.*, Capsule. *T.C.*, True cortex. *B.*, Central blood vessel. *F.C.*, Foetal cortex. *A.*, Fat-containing cell migrating centrally.

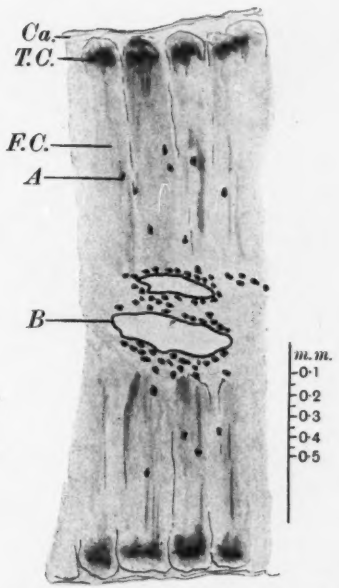

Diagram 12. Human foetal suprarenal 24 weeks (v.r. 215 mm.). Section stained for lipoid. *Ca.*, Capsule. *F.C.*, Foetal cortex. *B.*, Central blood vessel. *T.C.*, True cortex. *A.*, Fat-containing cell migrating centrally.

[1] A preliminary note on the distribution of lipoid in the gland and also on the earliest appearance of adrenin and of the chromaphil reaction was published in 1924 (22). Since then, with added material, many further observations have been made, and the present findings confirm the previous ones as far as they went.

Lipoid granules are seen in the 16-week embryo, in a few large cells that are migrating through the cortex and settling in the central part of the gland. The migration of these large lipoid-containing cells continues throughout

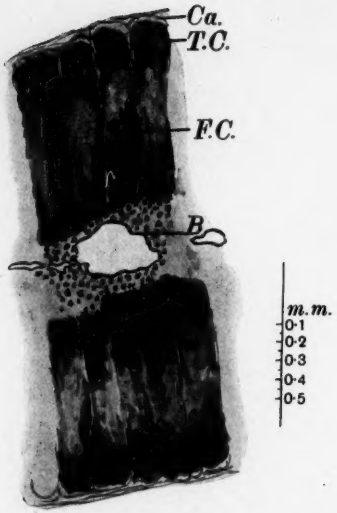

Diagram 13. Human foetal suprarenal 32 weeks (V.R. 284 mm.). Section stained for lipoid. *Ca.*, Capsule. *F.C.*, Foetal cortex. *T.C.*, True cortex. *B.*, Central blood vessel.

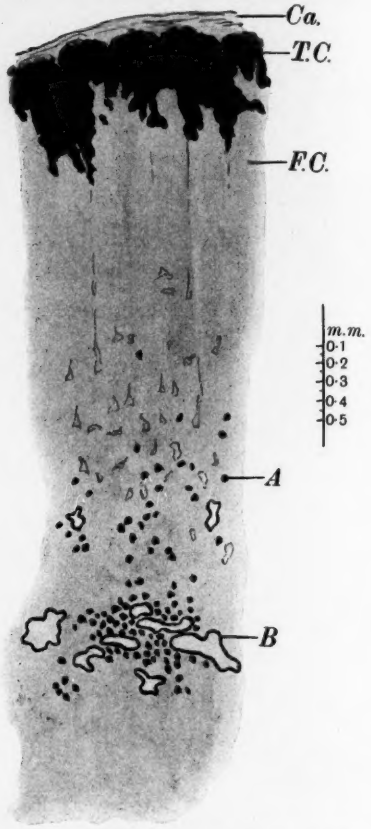

Diagram 14. Human foetal suprarenal, full time. Section stained for lipoid. *Ca.*, Capsule. *T.C.*, True cortex. *F.C.*, Foetal cortex degenerating. *A.*, Fat-containing cell migrating centrally. *B.*, Central blood vessel. (Half only of the cross-section is shown.)

foetal life, and they collect round the central blood vessels in ever-increasing numbers. The nature of these cells is not clear; they may be medullary cells or migrating cortical cells as suggested by Elliot and Armour (1).

The first trace of lipoid in cortical cells is found at 22 weeks when some of

the cells of the true cortex contain very small granules. By the 24th week the cells of the foetal cortex also contain very minute granules of lipoid, a section under a low magnification showing a diffuse pink staining throughout.

During the later months of foetal life the lipoid increases in amount, especially in the true cortex. As the foetal cortex degenerates its lipoid diminishes in quantity, although certain writers (7) speak of the "fatty degeneration" of these cells. At full time the "foetal cortex" contains no lipoid,

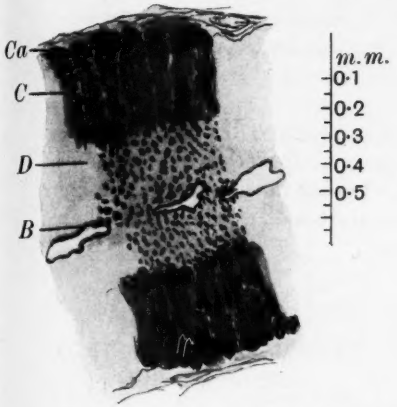

Diagram 15. Human suprarenal. Five weeks postnatal. Section stained for lipoid. *Ca.*, Capsule. *T.C.*, True cortex. *D.*, Remains of degenerating foetal cortex. *B.*, Central blood vessel.

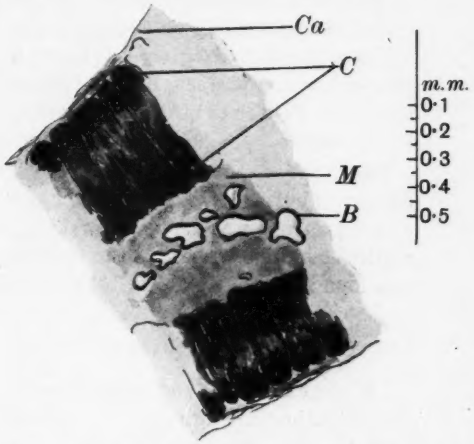

Diagram 16. Anencephalic human foetal suprarenal, full time. Section stained for lipoid. *Ca.*, Capsule. *C.*, Cortex. *M.*, Medulla. *B.*, Central blood vessel.

whereas the cells of the developing true cortex (which is invading and displacing the foetal cortex) show the lipoid stain in increasing amount especially in the actively growing layers.

After birth the lipoid staining corresponds to the development of the new cortex, so that at about three months a cross-section of the gland shows a well-marked lipoid reaction in the zona glomerulosa and fasciculata, and also in certain cells of the medullary region. Separating these two areas is a narrow band showing no fat, which corresponds to the region of the degenerating remains of the foetal cortex.

Chromaphil reaction and adrenin

It is generally accepted that there is some relation between the chromaphil reaction in cells and the presence of the active principle of the suprarenal medulla known as adrenin (13). In this investigation the chromaphil reaction was tested by two methods:

(1) Fixation of fresh material in formo-acetic-Müller.

(2) Ogata's method (8) of fixation in 5 per cent. $K_2Cr_2O_7$ followed by the addition of formalin.

The presence of adrenin was detected by making a 10 per cent. extract of the fresh gland in either 0·9 per cent. NaCl or Ringer's solution, and testing by some or all of the following reactions in frogs[1]:

(1) Vaso-constrictor effect on peripheral circulation by perfusion.
(2) Accelerator and tonic effect on heart by perfusion.
(3) Dilator effect on isolated eye.
(4) Secretor effect on cutaneous glands.

Chromaphil reaction. It was found that the chromaphil reaction was never obtained before 22 weeks of foetal life, but after this age the reaction was fairly constant. Failure to obtain the characteristic colour may be due in some cases to the material not being absolutely fresh.

Adrenin. Extract of the gland of a 12-week embryo (one case) contained a trace of adrenin (vaso-constrictor test only). At 16 weeks (three cases) the active principle was definitely present. At 18 weeks the extracts gave a more marked adrenin response to the tests used, and from this age onwards adrenin was found present in considerable amount.

Sympathetic chain and paraganglia

While examining the material some notes were made on the developing sympathetic elements, and are recorded here as confirming, for the greater part, the descriptions given by other workers (9, 17).

The sympathetic anlage is present in the 5 mm. embryo and consists of bilateral masses of cells lying in front of the developing vertebrae, and lateral to the aortae in sections showing these structures. The masses are differentiated from surrounding tissue by the darker staining of the nuclei of the cells.

In the 10 mm. embryo these masses consisting of one type of cell are seen in the same position, are better differentiated from the adjacent tissue, and contain nerve fibres.

In the 8-week embryos (30–40 mm.) sections show the developing ganglia to be composed chiefly of cells with small, darkly staining nuclei, and in addition a few larger faintly basophil cells with big faintly staining nuclei. A 12-week embryo shows these two types of cells, and moreover they are seen to be the same sort of cells as those that are invading the suprarenal gland.

The rosette arrangement already mentioned in connection with the masses migrating into the suprarenal (17) was seen in sections of a chain removed from a 16-week embryo.

In the 22-week embryo the nerve fibres are seen much more clearly, and the cells with large nuclei are definitely nerve cells of the sympathetic ganglia, and some show the distinctive surrounding nucleated sheath. As development

[1] N.B. We are indebted to Professor F. Ransom, M.D., and to Miss E. Scarborough, M.Sc., M.B., B.S., for the carrying out of these tests.

proceeds these cells gradually acquire more protoplasm, until at full time they have the characteristic appearance of the fully developed ganglion cell.

Paraganglia. The nerve cells of the semilunar ganglia acquire the adult type more quickly than those of the sympathetic chain, showing typical structure by 28 weeks. Neither in the sympathetic chain nor in the outlying ganglia has the chromaphil reaction been observed before full time (sections of material for the most part fixed in formo-acetic-Müller and stained with haematoxylin and Biebrich scarlet).

Zuckerkandl bodies. In the early embryo masses of cells derived from the sympathetic anlage grow forwards into the root of the mesentery together with nerve fibres; small bundles break off from these masses and invade the suprarenal gland, others form the semilunar ganglia, whilst yet others go to form the organs of Zuckerkandl.

The pre- and para-aortic tissue of a 16-week embryo from the region of the suprarenal glands is seen on section to contain the semilunar ganglia, collections of haemo-lymphoid tissue, and other encapsuled masses (the Zuckerkandl anlage) consisting of cells arranged in groups. These cells have large faintly staining nuclei, and although the cell boundaries are rather ill defined the cells are arranged in groups and are well supplied with capillaries. In embryos of 28 weeks these future Zuckerkandl masses are much larger, and the cells are irregular in shape and show a certain amount of fibrous tissue between the groups. At full time these bodies have the appearances described by Zuckerkandl (9). Under the high power of magnification the cells of the Zuckerkandl bodies at full time resemble the larger cells described in the suprarenal medulla, and like them show the chromaphil reaction in both protoplasm and nucleus. Fibrous tissue is increasing and the body presents the appearance of progressive atrophy, which becomes much more marked in specimens taken from a four-months-old infant.

The suprarenal in cases of abnormal foetal development

(1) *Anencephalic.* The organs of six specimens were examined, five full-time and one aged 24–26 weeks. Unless the specimen is hardened and fixed by injection of formo-saline through the umbilical vein it is difficult on account of its small size to isolate the suprarenal and clear it completely of the surrounding abundant fatty tissue. Thus only in one case of the six were the suprarenal glands weighed. The right gland weighed 0·35 gm., the left 0·27 gm. (average weight normal gland of the same age 4·78 gm.), giving weight ratios of 5280 and 6844 respectively (average weight ratios 748 and 679).

In section the full time glands show the feature described by Elliott and Armour (1), that is to say that traces only of foetal cortex are present in the specimens. On account of this absence of the foetal cortex the whole organ is thin. The true cortex is, however, thicker than in the normal full time foetus, and shows a well-marked zona glomerulosa and fasciculata, and in fact has the appearance of a 12-month post-natal gland, except that there is no sign

of the fibrous layer that is present at that time between the cortex and the medulla (diagram 17). The cells of the medulla show a well-marked chromaphil reaction, and the medulla appears normal except that it is rather more abundant than in the normal full time organ: this observation was also made by Meyer (20).

The distribution of lipoid is similar to that seen in the one 12-month postnatal gland examined for this substance, that is to say, all the cortex contains lipoid, and the reaction is especially well marked in the zona glomerulosa and in the deeper part of the zona fasciculata. It is however remarkable that the medulla shows no cells giving the lipoid reaction, a marked difference from the normal.

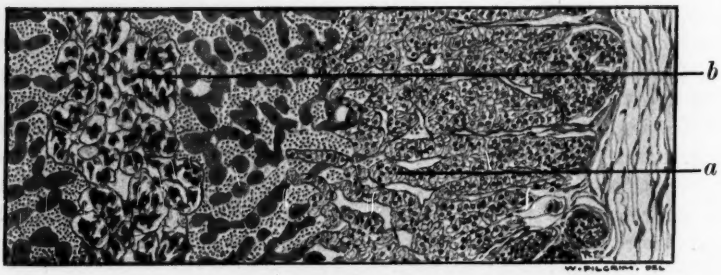

Diagram 17. Human anencephalic foetus (full time). Section through suprarenal showing (*a*) well-developed true cortex, (*b*) well-developed medulla.

The gland of the foetus aetat. 24–26 weeks is extremely small but consists of both true and foetal cortex. The cells of the latter are degenerating, and the true cortex is actively proliferating. Penetrating bundles are seen passing through to the central part of the gland. In this case anencephaly is associated with complete spina bifida.

The extract made from the gland of a 28-week anencephalic foetus not examined histologically contained adrenin as shown by all the four tests previously mentioned.

(2) *Monster.* A monster of about full time showing abnormal development of the external genitalia and neither anal nor genital apertures, was found on dissection to have an enormously distended uterus and no rectum; the ovaries were cystic. Further, there was complete absence of the thyroid gland, although serial sections of the neck showed parathyroids to be present. There was evidence that the thyroid gland had completely degenerated. In this case the suprarenal gland showed a relatively narrow and very inactive true cortex (diagram 18).

(3) *Osteogenesis imperfecta.* In a case of osteogenesis imperfecta the suprarenal gland was found normal in every respect, including the lipoid reaction.

(4) *Cerebro-meningocoele.* (*a*) A 32-week foetus showing the frontal lobes joined in the mid-line, but having well-developed sulci and gyri, and with most of the cerebellum in the hernia, presented a normal suprarenal gland.

(*b*) A 34-week foetus in which most of the brain, in a very degenerated condition, lay in the hernia, had the facies of an anencephalic, and the supra-

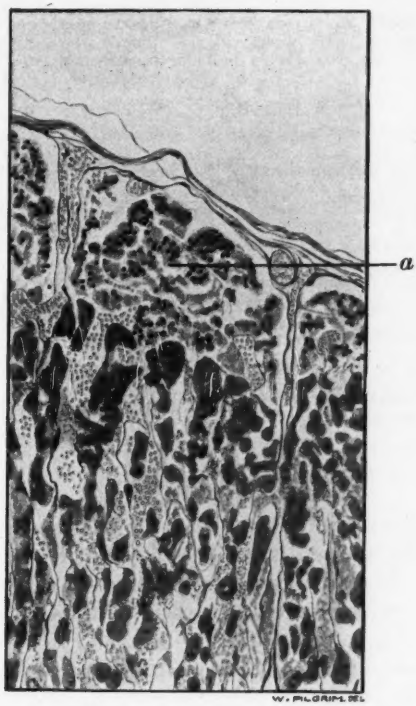

Diagram 18. Suprarenal of monster II. Note scarcity and inactivity of true cortex (*a*). Compare with diagram 9.

renal gland showed a marked diminution in the thickness of the "foetal cortex." This gland had the appearance of that of a 3-month infant, except for the absence of the fibrous layer normally found at that time between cortex and medulla.

(5) *Hydrocephaly and spina bifida.* A case of marked hydrocephaly and spina bifida showed normal development of the suprarenal gland.

The Suprarenal Gland in certain Pathological conditions.

	Condition	Age	Condition of gland
(*a*)	Mongol (1)	3 months post-natal	Normal
(*b*)	Status lymphaticus (1)	4 months post-natal	Normal
(*c*)	Erysipelas (1)	5 weeks post-natal	Cloudy swelling and cells looking unwell
(*d*)	Tubercular meningitis and miliary tubercular peritonitis (1)	9 months post-natal	Normally developed, showing caseous foci
(*e*)	Meningitis, secondary to osteomyelitis (1)	3 months post-natal	Normally developed, cells looking unwell
	FOETAL		
(*f*)	Pulmonary tuberculosis of mother (1)	21 weeks	Great excess of fat present in the foetal cortex
	Pulmonary tuberculosis of mother and father (1)	24 weeks	Ditto.
(*g*)	Syphilis of mother (3)	20–26 weeks	Excess of fat in the foetal cortex
(*h*)	Syphilis of mother (5)	Full time	No abnormal amount of fat

(Foetal Wasserman reactions not done.)

N.B. It has not been our aim to collect pathological material, but the cases quoted had to be classified from their history as "not normal," and a few notes were made as to the conditions found.

DISCUSSION

In addition to examining our own incomplete series of human embryos, we have had an opportunity also of studying preparations of embryos of 10 mm., 12 mm., 15 mm., 16 mm., and 25 mm. kindly lent us by Professor J. E. Frazer. In connection with the origin of the true and the foetal cortex our preparations are so strongly suggestive to us of an origin different from that usually accepted that we wish to put forward this view for consideration even though we are aware that there are many gaps in the evidence we present for its support. Our preparations suggested to us that the cap of proliferating coelomic epithelial cells seen in the 12 mm. embryo may represent the anlage of the true cortex. These cells appear to be pushing postero-laterally between the mesonephros and the suprarenal mass, which was seen to be differentiated in the 10 mm. embryo, and which would therefore represent the foetal cortex constituting the main mass of the gland throughout foetal life. In the 12 mm. embryo this suprarenal mass is limited posteriorly by a delicate connective tissue capsule, and on the medial aspect there is a procession of sympathochromaphil bundles, but no capsule. Zuckerkandl's diagram of the suprarenal of a 15 mm. embryo shows the aforesaid cap of cells separated from the main mass by a large vessel. This diagram, however, shows no differentiation between the cells forming the cap and those lying in the mesentery. Our sections which are cut less than 5μ thick show that these two are clearly

differentiated, and further that the cells of the epithelial cap are very similar to those in the genital ridge, but differ from the epithelium over the mesonephros.

The two parts of which the foetal suprarenal is composed—the true cortex which persists post-natally and the foetal cortex which atrophies after birth—are generally considered to have a common origin, differentiating from the cells forming the original mass seen in the 10 mm. embryo, but we suggest that this original mass forms only the foetal cortex, the true cortex arising from the cap of cells seen at a later stage. If these cells do form the true cortex they must push their way round between the connective tissue capsule and the main mass. This actual encircling of the suprarenal mass has not been traced but preparations of the 12 and the 18 mm. embryos are suggestive of the initiation of such a process.

Further, in support of our view of a different origin of the true and the foetal cortex is the following observation on the staining reactions of the cells. The suprarenal anlage is eosinophil even in the 10 mm. embryo and the cells of the foetal cortex are eosinophil throughout their persistence, whereas the cells of the true cortex differentiate after the appearance of the eosinophil anlage and never during foetal life give an acidophil reaction. We think it unlikely that small basophil cells, such as form the true cortex pre-natally, should differentiate from a mass of large eosinophil cells, and although many examples could be quoted of cells originally showing a basophil reaction subsequently becoming eosinophil we cannot recall any examples of the reverse process, although this has been described by de Beer (21).

The specimens lent us by Professor J. E. Frazer in our opinion supported this view of the possible origin of the true cortex except in the case of the 16 mm. embryo. The latter certainly showed some cells pushing round between the mesonephros and the suprarenal from the coelomic surface, but they were slightly flattened cells and appeared not unlike enlarged capsule cells. This 16 mm. embryo taken by itself would not have suggested the view put forward above.

With regard to the medulla of the gland our evidence agrees with the observations of others, namely, that it is derived from the sympathetic anlage. Its further development, however, as seen in our specimens does not entirely agree with the description given by Zuckerkandl (9). He describes the invading masses as composed of one type of cell only, namely, the "sympathoblasts," (smaller darkly staining type), except occasionally in foetuses of 50–60 mm. in which he observes a marked invasion of the gland by "chromaffinoblasts." We also noted this occurrence in one case aged 12 weeks. In addition, many of the invading bundles seen in our material contained even in embryos of about 8 weeks both types of cell, the smaller type being by far the more numerous until after the seventh month. This invasion by two types is also noted by other observers. There was no evidence that the migrating sympathochromaphil masses, when inside the gland, gave rise to ganglion cells as has

been stated (4); but ganglion cells were seen being carried into the gland with nerve fibres.

Hammar (18) has recently published an account of the human foetal suprarenal from the second month onwards, especially from the point of view of its functional activity. Comparing the foregoing evidence with his results it is found that he also notes that the time of invasion of sympatho-chromaphil masses occurs at about the 15 mm. stage. He finds "chromaffin cells" in an embryo of 90 mm., whereas we first obtained a chromaphil reaction at 22 weeks. (In this connection it is interesting to note that various observers mention the appearance of this reaction at stages of development ranging from 9 mm. to 7 months.) With respect to the lipoid, Hammar and other workers have found evidence of the presence of lipoid from 25 mm. onwards. We have been unable to investigate this point in embryos younger than 16 weeks, but in these (three cases) there was no trace of lipoid in the cortex.

The observations made as to the early atrophy of the foetal cortex in cases of anencephaly agree with those of Elliott and Armour, and later workers (20), but the suggestion that there is possibly some connection between the foetal cortex of the suprarenal and the development of the cerebral hemispheres is not supported by a specimen very kindly shown us by Professor J. E. Frazer. In this anencephalous embryo of 25 mm. the suprarenal is well developed and consists of the usual mass of foetal cortex and the narrow rim of developing true cortex. Moreover, our sections of the anencephalous suprarenal (24–26 weeks) showed a considerable amount of degenerating foetal cortex, though the gland as a whole was extremely small. It is interesting in this connection to note that in the case of cerebro-meningocoele (4 (*b*)) in which the brain is mostly degenerated the foetal cortex of the suprarenal gland was very much diminished, whereas in the other case (4 (*a*)) in which the cerebellum only was involved in the hernia the suprarenal gland was normal for its age. (See also Cosmettatos (10) on coexistence of malformations in brain and adrenals.) That the acephalous state is constantly associated with certain abnormal appearances of the suprarenal gland is indisputable, but the nature of the relationship is obscure.

Case II, the monster with the brain normally developed but with abnormalities of the genitalia, is certainly suggestive of some association between the true cortex of the suprarenal and the development of the genitalia (15), for in this case the true cortex was relatively narrow and inactive although the rest of the gland was normal. It must be remembered in this case, however, that another gross abnormality was present, namely, absence of the thyroid gland.

The question of the connection between adrenals and the sex organs has been fully discussed by Glynn (11, 14): Krabbe (12), however, regards any coexisting malformations of these organs as due to the close proximity of the derivative cells. Recently Rolleston (19) has given a classified description of cases of primary adrenal tumours, in many of which associated reproductive abnormalities were present.

SUMMARY

1. At 5 mm. the embryo shows the sympathetic anlage.

2. At 10 mm. the cortical anlage of the suprenal is evident.

3. At 25 mm. the suprarenal gland is defined and consists of true cortex, foetal cortex and immigrating sympatho-chromaphil bundles.

4. The immigration of the sympatho-chromaphil masses begins at about 12 mm. development, is most active between the 12th and 22nd weeks, and ceases about full time.

5. The foetal cortex degenerates progressively during the last 10 weeks of foetal life, although still forming the bulk of the gland at birth; it is replaced by a downgrowth of true cortex, the cells at full time already arranging themselves in columns (zona fasciculata).

6. The following changes occur during the first year: the foetal cortex has disappeared by the 12th month; the zona fasciculata is defined by the 3rd week; the zona reticulata is defined by the 14th week; the medulla gradually increases in amount.

7. Lipoid appears normally in foetal and true cortex at 24 weeks.

8. Adrenin appears at 12 weeks; the chromaphil reaction appears at 22 weeks.

We offer our sincere thanks to Lady Barrett, Miss Mabel Ramsay, Dr E. W. G. Masterman, Dr A. L. Baly, Miss Mouillin, Dr John Adams, Dr A. Wylie and to all others who have kindly sent us material. We are still anxious to increase our collection of embryos under 12 weeks.

We are indebted to Mr W. Pilgrim for some of the diagrams which he drew for us at very short notice.

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ON ANOVULAR FOLLICLES IN THE OVARIES OF THE STERILE DINGO AND THE AGED MOUSE

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League and Hartman (1925) have recently reviewed the literature relating to anovular follicles in the mammalian follicles possessing normal granulosa, basement membrane, and theca interna, but devoid of eggs, in the armadillo, opossum, and rhesus monkey. They distinguish, chiefly on the basis of size, three types of anovular graafian follicles, viz. primordial, medium and mature. In their opinion primordial anovular follicles are usually of approximately the same size as primordial ova and consist of granulosa cells only, loosely arranged within a basement membrane; as suggested by Gérard (1920) they arise from Pflüger's egg tubes and are simply groups of epithelial cells that have failed to become associated with ova. They concluded that in the opossum these primordial anovular follicles may undergo cell division and enlarge to form "medium" anovular follicles consisting of many compactly massed granulosa cells, as Régaud and Lacassagne (1913) maintain to be the case in the rabbit. Another type of anovular follicles is that which arises by death and resorption of the ovum, or more rarely by the migration of the ovum out of the membrana granulosa. League and Hartman hold that in the opossum this type gives origin to the mature anovular follicles whose structure has the appearance of a syncytium and whose nuclei are mostly peripherally arranged, with a scattering of several nuclei near the centre.

They concluded also that the identity of the origin of the normal and the anovular follicles is evidenced by their association together in similar stages of development. Two follicles, one normal, the other abnormal, may be surrounded by the same theca interna. They hold that the anovular follicle undergoes chromatolytic and lipolytic degeneration and present evidence to show that the granulosa is able to maintain its integrity for some time after the egg has disappeared. Régaud and Lacassagne (1913) state that the anovular follicles are to be found only in young animals and that their number decreases with the age of the individual. On the other hand, Gérard states that in the case of *Galago* the anovular follicles are few in number in the young and numerous in the adult, and League and Hartman maintain that the anovular follicles are not limited to young animals.

The present writer, in the course of an examination of sterile dingoes and of mice during their sixth pregnancy for other purposes, took the opportunity of looking for anovular follicles. The ovarian tissue was fixed in Allen's Bouin and Flemming and stained with Delafield and Heidenhain's haematoxylin.

Serial sections of 8μ were examined. In certain details the results of this study agree with the conclusions of League and Hartman, while in others they do not.

In the case of the adult sterile dingo bitches, numerous primordial follicles were found; while most of them showed degeneration of the contained ovum, and a few were normal, the primordial anovular follicles described by League and Hartman were exceedingly rare, and in contradistinction to the findings of the above authors, no signs of mitotic figures were to be found. Mitotic figures in early stages, however, were found in the primordial follicles in which the ovum had already degenerated or resorbed, and which had a normal active membrana granulosa.

The most common type of anovular follicles in the dingo is that whose structure is very similar to the structure of the "mature" anovular follicles described by League and Hartman. However, they are found to vary greatly in size, ranging from 0·069 mm. to 0·19 mm. in diameter in the largest section (fig. 1). No follicles resembling in structure the so-called "medium" anovular follicles of League and Hartman could be identified, and no evidence could be gleaned that would support the contention of the above authors and of Régaud and Lacassagne (1913) that such medium anovular follicles had in the case of the dingo bitches developed by cell division from the primordial epithelial cells. The condition found suggested that these anovular follicles in the dingo had resulted from the absorption of the ova and preservation of membrane granulosa at a stage when the follicle was of the size that it exhibited at the time of examination. Various stages of mitotic figures were found in the follicles in which the ovum had degenerated or already become resorbed while their membrana granulosa corresponded with that of normal follicles at a similar stage of development. In some cases the granulosa projects into the lumen and mitotic figures in early stages are still showing and in the case of a more advanced stage of degeneration the granulosa cells are scattered loosely in the lumen, and there is an indication of an antrum in the centre of the follicle, as described by League and Hartman, in the case of mature anovular follicles. In other cases the anovular follicles in the course of formation become compressed from both sides and elongate, taking on a tubule-like appearance (fig. 2). Structures identical in appearance with the "medium" follicles of League and Hartman and surrounded by a well-developed theca interna were present, but on careful examination of the serial sections these were found to be merely parts of a normal medium-sized follicle.

Careful examination of serial sections failed to reveal the presence of two follicles, one normal and the other anovular, in association as described by League and Hartman. On the other hand, there was plentiful evidence to show that such an apparent combination was obtained when sections were cut from a single follicle which had become diminished in size, for what seems to be two follicles when followed through was found to be but one (fig. 2).

The fate of these anovular follicles was typical lipolytic degeneration; several single anovular follicles of varying size had undergone lipolytic

degeneration here and there, but it was found that the great majority migrated to one area of the ovary which consisted of nothing else but follicles in some stage of degeneration (fig. 3).

In the left ovary of one of the dingoes masses of tissue closely resembling seminiferous tubules were found invading the connective tissue (fig. 4). It was not possible to decide with confidence what this tissue actually was. No signs of spermatogenesis could be identified, but the structure was very similar to that of the testis of the immature male and very different from that of the anovular follicle. The theca of the abnormally large atretic follicles, particularly when contorted and enclosing a lumen lined with degenerated granulosa, presented an appearance very suggestive of this seminiferous tubule-like tissue, but it is impossible to decide whether the seminiferous tubule-like tissue had its origin in this.

It is of interest to note that Hammond (1925) describes a very similar embryonic seminiferous tubule-like tissue in the ovaries of infecund rabbits. His figures (Pl. XII, fig. 2, and Pl. XIII, figs. 3 and 4) present features that are very similar indeed to anovular follicles found in the dingoes.

In the case of the old pregnant mice, numerous anovular follicles were found in the ovaries (fig. 5), whereas in the case of younger mice pregnant for the first or second time, no such follicles were present. In the mouse it would seem that the number of anovular follicles increases with age after a certain age. This is not in agreement with the conclusions of Régaud and Lacassagne. In structure these follicles were as the primordial and medium anovular follicles described by League and Hartman.

Since, in the experience of the writer, anovular follicles are more frequently found in old, sterile, or pregnant individuals, it seems reasonable to suggest that their development is determined by nutritional agencies, and that when nutrition or the hypothetical "generative ferment" of Heape is inadequate, it may result in the failure of many of the constituent follicles of the ovary to attain their normal development and the appearance of anovular follicles. It is probable that in this matter one or more members of the endocrine chain are involved. In the case of the dingoes examined the individuals were infecund and examination of the endocrines revealed the fact that all were abnormal (Tamura, 1926). However, it is impossible to say definitely that nutritive supply or the "generative ferment" has its origin in the endocrine organs, but it may be assumed that, as suggested by Hammond (1925), endocrine organs have a very important rôle in the normal development of the ovary.

It is still questionable whether it is the gonads or the other endocrine organs that are the first to be affected by environment. However, Glynn (1921) and Masui and Tamura (1924) have presented evidence which demonstrates the intimate interrelationship of the adrenal and ovary, and McCarrison (1917) of the thyroid and the gonad. Therefore it may be suggested that the formation of anovular follicles may be the sequel to a malfunctioning of some member of the endocrine chain caused by an inadequate nutrition or "generative ferment."

In conditions of inadequate nutrition fewer primordial follicles continue their development to become medium-sized follicles than in conditions when nutrition is in every way adequate and similarly fewer medium-sized follicles continue their development to become large-sized follicles and further fewer of these proceed to complete development. The result is, therefore, that in such a case, fewer ripe ova are elaborated and this is evidenced by the fact that very few corpora lutea are found on examination. In the case of the dingoes, there were no corpora lutea.

I am greatly indebted to Dr F. A. E. Crew for the material supplied and also for much constructive criticism during the course of this study. I also wish to thank Dr A. W. Greenwood for his valuable help.

DESCRIPTION OF PLATE

Fig. 1 shows various sized anovular follicles the structure of which is the same as that of "mature" anovular follicles of League and Hartman. Note few normal small-sized follicles in the peripheral region.

Fig. 2 shows two follicles surrounded by the same theca interna, and an elongated anovular follicle.

Fig. 3 shows a group of anovular follicles which are undergoing lipolytic degeneration.

Fig. 4 shows a seminiferous tubule-like mass which is found in the left ovary of a dingo bitch.

Fig. 5 shows anovular follicles found in a pregnant mouse.

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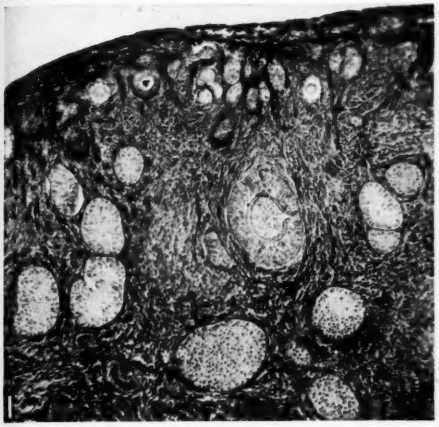

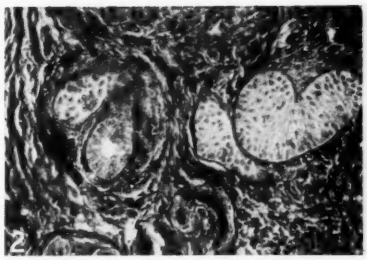

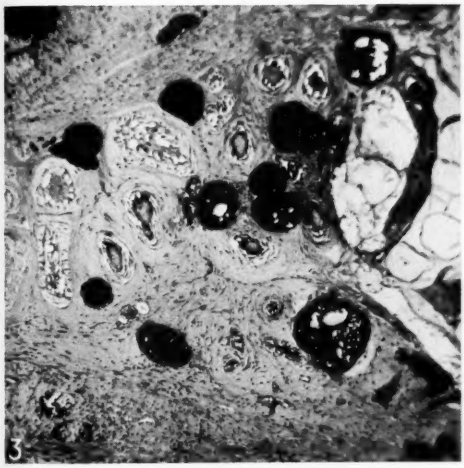

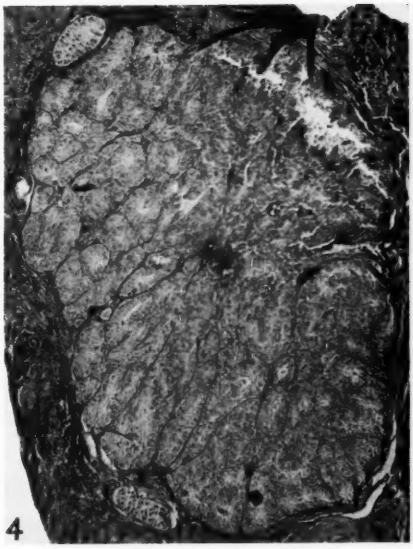

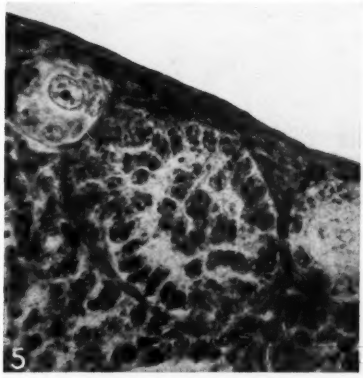

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A CASE OF SUPERFOETATION IN THE PIG

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1. INTRODUCTION

What would appear to be a case of superfoetation in the pig occurred recently in a herd belonging to Mr Henry Alexander, Bo'ness, Scotland. The history, verified by the writer after interviewing the owner, his employees, some neighbours, and also after personal examination of the animals concerned, is as follows.

A pure-bred Large Black sow aged 2 years and a few days gave birth on Wednesday, June 16th, 1926, to a litter of 4. Some 3 weeks after this her owner noticed that she was unusually well filled out for a sow which had recently given birth to a litter, but regarded this as evidence that she was a good milker. This suggestion, however, he did not confirm by examination. Exactly 31 days after the birth of this litter, on the morning of Saturday, July 17th, she gave birth to a further litter of 10. None of the pigs of either litter was in any way abnormal. Five of the second litter were, however, killed by the owner within 2 days of farrowing, for the reason that in his opinion the sow had not sufficient nourishment for them all.

The practice of mating sows employed by Mr Alexander was to let them run in a pen with a boar after weaning. In this case the Large Black sow ran with a Middle White boar for a period of approximately 3 months, by which time the owner said it was obvious that she was pregnant, and in the beginning of May he removed her to a sty by herself.

Unfortunately, the pigs were not weighed at birth, as the case was not reported until some time after. However, on August 4th, the first litter, which was then 48 days old and had been sold to a neighbour, averaged 19 pounds, while on the same day the second litter, now consisting of only 5 individuals, aged 17 days, averaged 9 pounds. On August 27th, the two litters, aged 72 and 41 days, weighed on an average 34 and 15 pounds respectively. The second litter did not do very well as the sow became short of milk. They were weaned at the age of 33 days. These weights are somewhat below the average usually obtained by similar cross-matings on this farm. All the pigs were of the type commonly associated with the Middle White × Large Black cross. There were no other litters on the farm of corresponding ages. The owner and his wife observed the sow in the actual process of farrowing on each occasion.

2. DISCUSSION

The sow is polyoestrous and this Large Black probably took the boar about 11 or 12 weeks after her previous parturition on December 3rd, when she had given birth to a litter of 9. Therefore the conception associated with the litter of 4 occurred in February. The sow was not removed from the boar till May.

According to Fleming (quoted by Marshall), the dioestrous cycle of the sow is from 2 to 4 weeks, though it is generally accepted as being around 20 days. It would appear that, in this case, the sow conceived to the first service but came in season again after a period of about 30 days which was somewhat longer than normal though by no means extraordinary, with the probable result that the conception associated with the litter of 10 occurred in March.

Cases of alleged superfoetation have been reported by Harman (1917, 1918) in the cat and in the cow; Hunt (1919) in the cat; Ingram-Johnson (1921) in the human; King (1913) in the rat; Kroon (1897) in the goat; Marshall (1922) in the cat; Sumner (1916) in the mouse; and Tapken (1890) in the sow. However, Kuntz (1920) has shown that in cases where a small foetus is delivered at the same time as a normal one, the probability is that it is due not to superfecundation or superfoetation but to intra-uterine death under circumstances in which, although extensive necrosis of the tissues occurs, very little absorption takes place, with the result that the external form of the foetus remains apparently well preserved and intact for a relatively longer period than usually intervenes between the death of such foetuses and the termination of pregnancy. Kuntz, dealing with three cases (two in the cat and one in the dog), which to the casual observer might have been attributed to superfoetation, shows clearly, by determining that all the foetuses present in the uterus were in the same phase of development during the early part of gestation, that they were instances of intra-uterine death and concludes that the great majority of reported cases of superfoetation may be interpreted in this way rather than on the assumption that one or more ova were fertilised and implanted in a uterus which was already pregnant with one or more foetuses in a more or less advanced stage of development.

All these cases, with the exception of the one in the sow, might be explained on the hypothesis put forward by Kuntz. The sow reported by Tapken was mated on February 22nd and again 17 days later. On June 17th, 120 days from the first mating, she gave birth to 7 live pigs and 14 days later to 9 live and 3 dead pigs. This is similar to the case under review but with a shorter interval and therefore not so definite.

It is equally impossible to explain by Kuntz's hypothesis the present case of the Large Black sow. In the first place, the two sets of foetuses were born with an interval amounting approximately to the dioestrous cycle. In the second place, neither the offspring of the first nor of the second parturition differed in

any way from the normal progeny of such a cross; they showed no signs of either under- or over-development, and it therefore must be concluded that the two litters were conceived at two different times, the difference being equal to the dioestrous cycle. While it is not uncommon for sows to come in heat again about 3 weeks after ovulation has occurred, it is extremely rare that ovulation accompanies such an oestrous period. The cervix of the sow is very slightly defined and there appears to be practically no uterine seal of pregnancy. Mr A. Walton, of Cambridge University, has informed the writer that after many observations with a full-grown boar on a medium or small-sized sow he had come to the conclusion that the penis does occasionally penetrate the cervix.

Whether each litter was located in a separate horn must remain a matter of conjecture. Warwick (1926) has, however, shown that in the sow internal migration of the fertilised ovum occurs and that some mechanism operates to produce a more or less equal distribution of the ova between the two horns; although it appears possible to get the ova congregating in one horn with a very few in the other. This, however, need not be regarded as essential. At the same time, it is worth noting that if such was the case, one would normally expect that the uterine contractions at the birth of the first litter would produce abortion of the second. If the two litters were located in different horns, then it appears from this case and that of Tapken that in the pig there is a considerable lack of co-ordination between uterine horns in various stages of pregnancy.

The cases here recorded can be explained by the assumption that the eggs from which the two litters originated were fertilised at different times. The eggs may have been liberated at the same ovulation. If this were so, then they could have been fertilised by spermatozoa introduced by separate coitions (superfecundation), or, on the other hand, a second ovulation followed by fertilisation may have taken place during pregnancy (superfoetation), and such ova may have been fertilised by sperms introduced at the first copulation which were still alive and functional during the subsequent ovulation, or else by spermatozoa introduced at a subsequent copulation during the course of pregnancy. If this were the case, then the eggs liberated by the second ovulation and subsequently fertilised, were located in one horn, or else the sperms were by some means able to pass the month-old embryos and fertilise the new ova, the resulting foetuses succeeding in remaining in place when the sow gave birth to the first 4. From the facts stated above, it would appear that either of these latter alternatives of superfoetation furnishes the explanation of this abnormal case.

3. SUMMARY

1. A Large Black sow gave birth to a litter of 4 and a month later to another litter of 10.

2. Previous reports of superfoetation in the human, cat, cow, rat, mouse, dog, goat, and pig are discussed.

3. It is shown that the hypothesis of Kuntz that these were not cases of superfoetation but of arrested embryonic development may hold good for all these cases with the exception of the one in the pig reported by Tapken and the case under review.

4. Attention is drawn to the fact that in the sow there may be a considerable lack of co-ordination between the uterine horns in various stages of pregnancy.

5. Whether this is a case of superfecundation or of superfoetation is discussed. The writer suggests that most probably it is a case of superfoetation since the period between the birth of the two litters is somewhat greater than the normal period of the dioestrous cycle.

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The writer wishes to thank Dr F. A. E. Crew for his criticism and advice.

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A CASE OF RIGHT-SIDED AORTIC ARCH AND PERSISTENT LEFT SUPERIOR VENA CAVA

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Abnormalities of the aortic arch are of embryological interest and are described in the standard text-books of anatomy.

The variation described in this paper, however, appears to be sufficiently interesting to warrant a full and detailed account, as it presents the rare combination of an aorta developing from the right fourth arch and the persistence of the left anterior cardinal vein forming a left superior vena cava. Other arterial and venous abnormalities present in the same subject will also be described.

The subject in whom these variations appeared was a female aged 53 who died from cerebral haemorrhage in a Melbourne hospital and was admitted to the Anatomical Department of this University.

Attention was first drawn to the abnormal circulatory system by the discovery, on opening the skull, of a large aneurism of the basilar artery. The sac had ruptured causing death.

The examination of the heart and great vessels displayed a complete departure from the normal in the origin and relations of the structures about the upper thorax and neck.

The ascending aorta commenced in the left ventricle dorsal to the origin of the pulmonary artery. It passed cranially and to the right for a distance of 8 cm. (being thus longer than usual), and became continuous with the ascending aortic arch. The transverse arch passed dorsal to the trachea and oesophagus, becoming continuous with the descending arch and thoracic aorta which lay in its normal position to the left of the vertebral column.

The pulmonary artery was 2·5 cm. in length, thus being shorter than usual (*vide infra*).

The branches and relations of the aortic arch were as follows:

Branches

(*a*) At the commencement of the arch the left common carotid passed transversely ventral to the trachea and then turned cranially, accompanied by the left vagus. At the point of origin of the left common carotid was a

smaller artery passing cranially, possibly a thyroidea ima. This point could not be determined accurately as the dissectors had removed the structures in the neck.

(*b*) The next great vessel from the arch was the right common carotid arising at the junction of the ascending and transverse arch.

(*c*) The right subclavian arose from the summit of the arch.

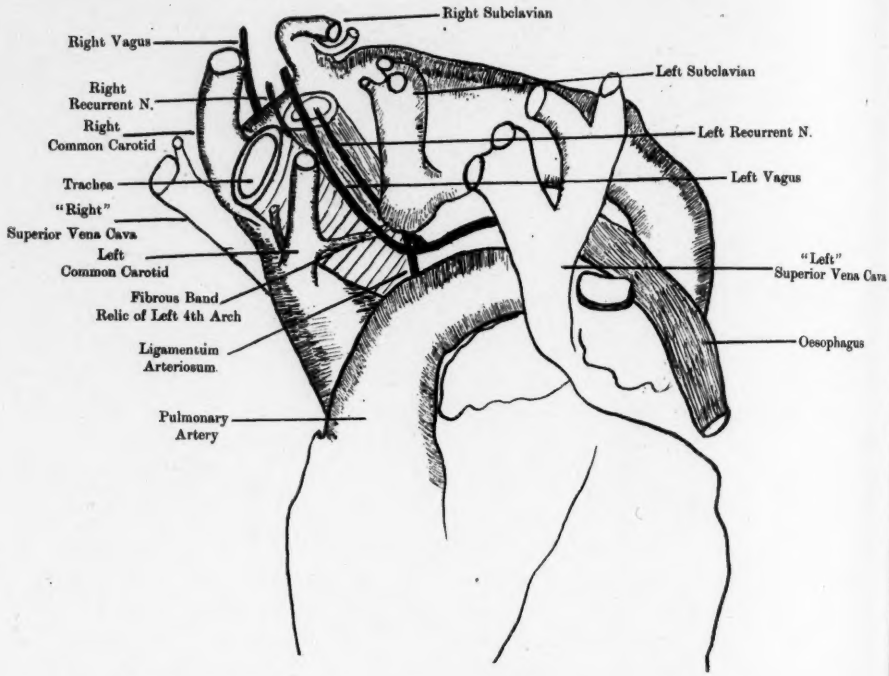

Fig. 1. Aorta and branches (anterior view). Right and left superior vena cava.

(*d*) The left subclavian artery had its origin from the ventral aspect of the junction of the descending arch and the thoracic aorta. This vessel was connected with the pulmonary artery by a stout fibrous band—the ligamentum arteriosum. It was also united to the left common carotid artery by a stout band of fibrous tissue 3 mm. in diameter, which was probably the remains of the left fourth arch.

The vertebral arteries arose from the right and left subclavians respectively and were thus normal in origin.

Relations

To the right and slightly dorsal to the ascending aorta was the superior vena cava opening into the right atrium.

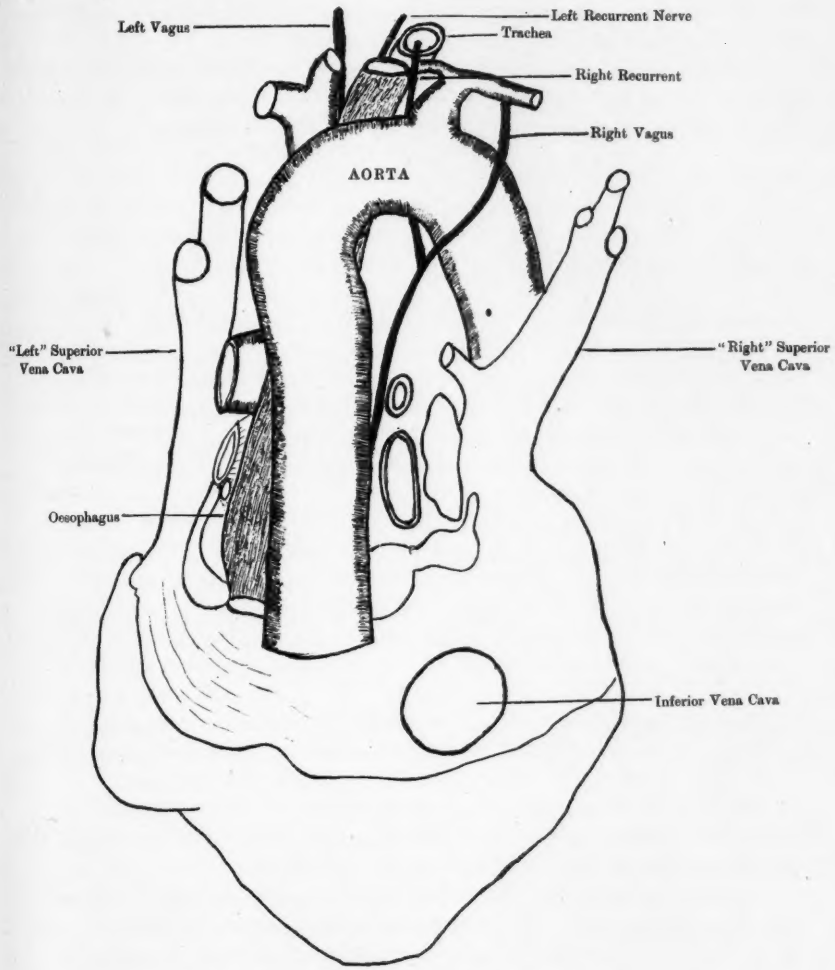

Fig. 2. Heart and great vessels (posterior view).

To the left of the arch and passing along the coronary sulcus was a vessel equal in size to the superior vena cava. This left superior vena cava opened into the coronary sinus.

The coronary sinus was a large cavity 2·5 cm. in diameter and 6 cm. in length, which passed into the right atrium without any clear demarcation.

The inferior vena cava opened into the right atrium without any deviation from normal.

A fibrous band passed transversely from the left superior vena cava to the right superior vena cava. Opening into the left superior vena cava was a small vein, probably a superior intercostal vessel.

The right vagus nerve passed dorso-laterally to the aortic arch, and the recurrent nerve, passing ventrally below the arch, occupied a position in front of the latter and between the trachea and the oesophagus.

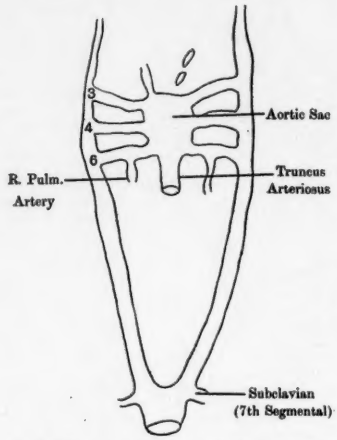

Fig. 3. Diagram showing relations of aortic arch vessels before modification takes place.

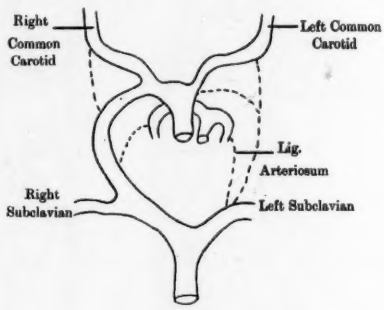

Fig. 4. Diagram showing the changes which have taken place, resulting in the abnormality described in the text.

The left vagus passed ventral to the left subclavian artery and gave off its recurrent branch caudal to the ductus arteriosus, the nerve then passing to its usual position.

Other arterial abnormalities present were:

Absence of the coeliac axis. Superior mesenteric artery gave off the hepatic artery. The splenic artery arose from the aorta.

Venous abnormalities. The inferior vena cava bifurcated on the cranial side of the right common iliac artery and the two parts united together again distal to that vessel. The cephalic vein was absent on the left side.

Numerous cases are on record showing the presence of a right aortic arch, but in the literature at our disposal we have been unable to find a record of a case showing both these abnormalities present in the one subject. The fact that each of these abnormalities frequently occurs singly seems to show that their occurrence together in this instance was merely a coincidence and that

the appearance of one abnormality had no causal relationship to the development of the other.

Quain describes two types of right aortic arch, the commoner being that here described; the less common type presents a left innominate, a right common carotid and a right subclavian. Douglas Reid in the *Journal of Anatomy and Physiology* described three cases, two belonging to the common type and the third to the second or rarer type. The case here recorded belongs to the commoner type of right aortic arch. It also showed a well-marked fibrous remnant representing the remains of the left aortic arch and connecting the junction of the left subclavian and ductus arteriosus with the origin of the left common carotid from the aorta.

Congdon, in *Contributions to Embryology*, described fully the development of the branchial arch system in the human embryo, basing his conclusions on a study of human embryos ranging in length from 1·3 to 24 mm. Although in the main his work confirms that of Rathke, he has made several important observations:

1. The truncus instead of dividing into two ventral aortae, as is usually described, opens into an expanded chamber, the aortic sac. From the sac arise the branchial arch vessels which then pass through the visceral arches to reach the dorsal aortae. The external carotids, formerly considered to be derived from the ventral aortae, are secondary outgrowths from the aortic sac.

2. He also draws attention to the fact that the first two arches early disappear and that, during the branchial period, the blood from the truncus reaches the dorsal aorta along the following successive paths—first arch, first and second arch, second and third arches, third and fourth arches, third, fourth and sixth arches, and, not rarely, the last three in company with the so-called fifth arch. At the end of the branchial period then the branchial system is represented by the aortic sac, third, fourth and sixth arches passing to the dorsal aorta. From the sixth arch arise the pulmonary vessels going to the developing lungs.

The breaking up of the arch system is due to interruption at four places and these interruptions are determined by two main factors:

1. Diminished blood supply.
2. Longitudinal tension due to the downward migration of the heart.

(*a*) Loss of dorsal aorta between third and fourth arches due to stagnation at this point because the stream in the dorsal aorta, cranial and caudal to this spot, flows in opposite directions.

(*b*) Degeneration of right arch between pulmonary artery and dorsal aorta because it receives less blood than the left owing to the obliquity of the pulmonary artery.

(*c*) Cutting off of the right paired aorta at its lower end. This is reduced because the sixth arch has become interrupted and the aortic, owing to its obliquity, is directing its current more to the left than into the right fourth arch.

It would seem, therefore, that the persistence of a right fourth arch would arise from an abnormal division of the truncus arteriosus, whereby the aorta, instead of being directed obliquely towards the left fourth arch is directed more to the right. This could be caused by abnormal development of the septum which divides the truncus into aorta and pulmonary artery, and is suggested in this case by the marked alteration in the relative lengths of the ascending aorta and the pulmonary artery.

If this were the only abnormality present, the arch of the aorta would then be formed by the aortic trunk, right half of aortic sac, right fourth arch, right dorsal aorta below fourth arch, and its branches would be in order; left innominate (from left half of aortic sac), right common carotid and right subclavian. This is the order of branches in the smaller group of cases of persistent right aortic arch. But in the case under discussion the order of branches is: left common carotid, right common carotid, right subclavian and left subclavian. In all probability then, in this instance, the aorta has been formed by the truncus, the whole of the aortic sac, right fourth arch and dorsal aorta caudal to this, and the left subclavian has been formed by the seventh segmental vessel and the small terminal portion of the left dorsal aorta.

The remaining part of the left dorsal aorta is represented by the fibrous cord mentioned above. A right subclavian artery arising in this way is fairly common and is very fully discussed by Cairney.

The presence of the left superior vena cava has been frequently reported in the literature. McCotter collected 120 cases and classified them as follows:

1.	Double superior vena cava without anastomosis ...	64
2.	,, ,, with small anastomosis ...	14
3.	,, ,, ,, normal anastomosis ...	18
4.	Left superior vena cava without right S.V.C.	12
5.	Unclassified	12

In the case under discussion both venae cavae were present and were united together by a fibrous band representing the remains of the left innominate vein. Opening into the left vena cava just caudal to the fibrous band was a small vein probably representing the superior intercostal. This could not be definitely determined as it had been divided close to its termination by the dissectors, and the present writers had no opportunity of studying the structures *in situ*.

Hutton reported a very interesting case in which the left superior vena cava ended in continuity with the coronary sinus. The coronary sinus, however, did not open into the right atrium but its blood reached the right superior vena cava *via* a left innominate vein.

The left superior vena cava is derived from the caudal portion of the left anterior cardinal vein. Normally this portion becomes transformed into the oblique vein of Marshall, the vestigial fold of Marshall and the vertical portion of the superior intercostal vein. Cameron states that the gap between the two

latter structures is bridged across by a small vein which is constantly present in normal subjects. The left superior vena cava, according to this view, would therefore be represented by the following structures establishing a communication between the left innominate and the coronary sinus, namely, the vertical portion of the superior intercostal vein, the small unnamed venule, the vestigial fold of Marshall and the oblique vein of Marshall. The left phrenic nerve is normally in close relationship to these structures and it is interesting to note that in the case under consideration the left phrenic was in close association with the persistent left superior vena cava.

The presence of abnormalities in widely separated parts of the vascular system is well illustrated in this case. Congdon stresses the marked effect produced by local variations in the development of neighbouring organs in determining abnormalities in the vascular system. In this case, however, in view of the widespread abnormalities, it would seem that the determining factor must be looked for during the earlier period of development and may be even inherent in the germ cell itself.

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A NOTE ON TWO ABNORMAL LARYNGEAL MUSCLES IN A ZULU

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Charles, a Zulu labourer, aged 69, died of pulmonary tuberculosis on September 2nd, 1925. His body was dissected in the Department of Anatomy of the University of the Witwatersrand, Johannesburg.

In the course of the dissection there were observed, in addition to various pathological conditions, numerous structural abnormalities not referable to pathological causes. Of the pathological conditions, the principal were advanced pulmonary tuberculosis accompanied by enlargement of the right atrium of the heart, duodenal ulcer, and degenerative changes in the small intestine, accompanied by widespread haemorrhages into the submucous coat, which were regarded by Dr A. Sutherland Strachan, Senior Lecturer in Pathology, as due to anthrax. There were also present an enlarged liver, complete fibrosis of the left vertebral artery, and appearances in the kidney suggesting parenchymatous nephritis.

Among the abnormalities observed were the following: The hemiazygos vein emerged from the substance of the kidney near the upper pole, and formed with the accessory hemiazygos and left superior intercostal veins a continuous venous trunk opening into the left innominate vein. On the left side the subscapular and posterior circumflex humeral arteries had a common origin from the third part of the axillary artery. On the right side the subscapular artery arose from the second part of the axillary artery instead of from the third part. On the right side also the radial artery divided into its two terminal branches some distance proximal to the wrist joint. In the right leg the relative size of the posterior tibial and peroneal arteries was reversed, and the communicating artery connecting them distally was greatly enlarged. Abnormal vascular arrangements of the above nature have been described in Cunningham's *Textbook of Anatomy, passim.* In the right foot the flexor digitorum brevis muscle had only three tendons of insertion instead of four. They were inserted into the second, third and fourth digits. A small partly fleshy and partly tendinous fusiform slip arose from the tendon of the flexor digitorum longus, and divided into two very slender tendons of which the medial blended with the tendon of the flexor digitorum brevis to the fourth digit, while the lateral passed to the fifth digit. In its course it lay superficial to the tendon of the flexor digitorum longus to that digit, and was inserted in exactly the same manner as the normal tendons of the flexor digitorum brevis. This slip is of some anthropological interest, as it is a vestigial representative of the

deep head of the flexor digitorum brevis, which is said to be present in monotremes, marsupials and all primates below man (***Quain's Anatomy***, Vol. IV, Pt. 2).

More recently, in the dissection of the larynx, two abnormal muscular slips were observed which were thought worthy of more detailed notice, as no similar arrangements are described in any of the texts available to us here.

On the posterior aspect of the larynx, on the right side, a muscle was observed arising, in continuity with the origin of the posterior crico-arytenoid muscle, from the uppermost part of the depression lateral to the median ridge

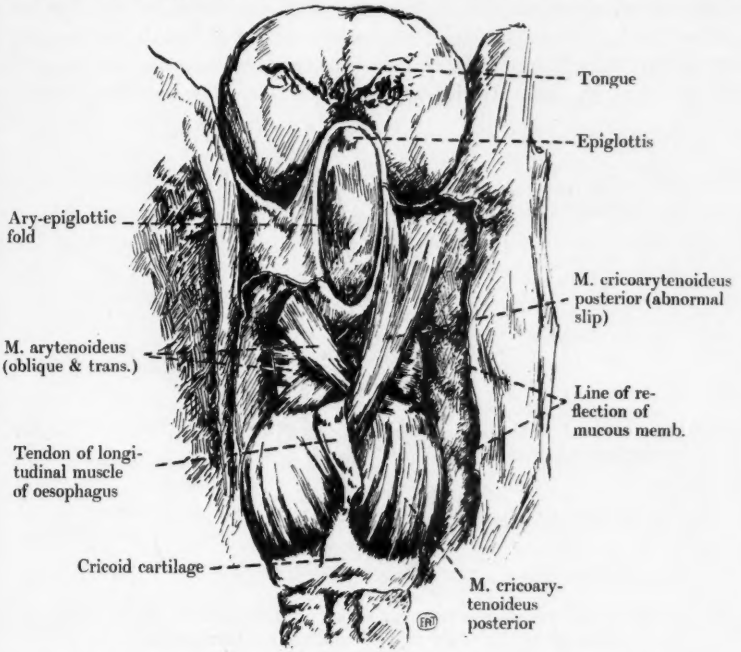

Fig. 1. Posterior view of dissection of larynx, showing the abnormal slip of M. cricoarytenoideus posterior.

on the posterior aspect of the left lamina of the cricoid cartilage. From this origin the muscle passed upwards and laterally, superficial to the oblique and transverse arytenoid muscles, to find its principal insertion, in common with the oblique arytenoid muscle, into the apex of the arytenoid cartilage. Some of the medial fibres of the muscle, however, were inserted into the mucous membrane of the ary-epiglottic fold, while a few on the lateral side turned laterally to blend with the transverse arytenoid muscle.

Fig. 1, which was drawn from the specimen, shows the dissection from the posterior aspect. It shows the origin of the muscle from the lamina of the

cricoid cartilage, superior to and in continuity with the origin of the posterior crico-arytenoid muscle, and lateral to the attachment of the tendon of the oesophageal longitudinal muscle. The muscle lies superficial to the arytenoid muscles as it ascends obliquely to its insertion into the arytenoid cartilage, where it is in continuity with the origin of the ary-epiglottic muscle. The muscle is innervated by a twig from the posterior division of the inferior laryngeal nerve. Its vascular supply was not accurately determined, owing to the fragile condition of the specimen, but it was apparently derived from the superior laryngeal artery.

The second of the abnormal muscular slips was found on the left lateral aspect of the larynx, under cover of the left lamina of the thyreoid cartilage. It arose from the left supero-lateral angle of the lamina of the cricoid cartilage under cover of the lateral crico-arytenoid muscle, and passed upwards and

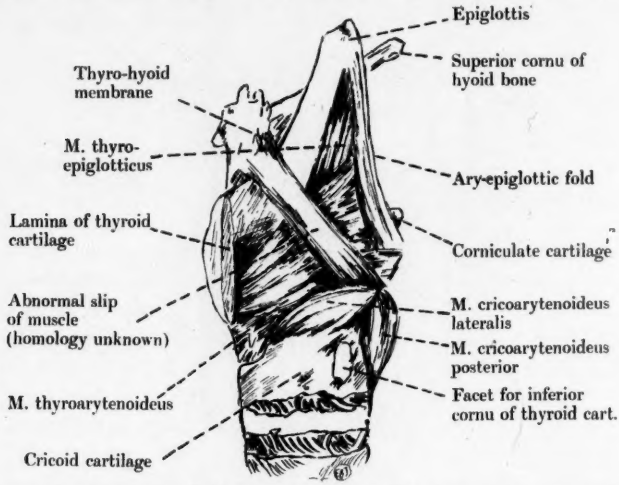

Fig. 2. Lateral view of dissection of larynx, showing abnormal muscle of unknown homologies. The left lamina of the thyroid cartilage has been removed.

anteriorly, lying superficial to the thyreo-arytenoid and thyreo-epiglottic muscles, to be inserted into a thickened band of fascia which appeared to be continued above into the lateral part of the middle thyreo-hyoid ligament.

Fig. 2, which was drawn from the specimen, shows the dissection from the left lateral aspect, the left lamina of the thyreoid cartilage having been removed in order to expose the muscles. The abnormal slip is seen emerging from under cover of the lateral crico-arytenoid muscle, which conceals its origin, and crossing obliquely, superficial to the thyreo-arytenoid and thyreo-epiglottic muscles. The continuity of the fascial insertion of the muscle with the middle thyreo-hyoid ligament is also well shown. The muscle was innervated by the anterior branch of the inferior laryngeal nerve. The fragile

condition of the specimen prevented any accurate determination of the arterial supply of the muscle.

It does not appear from the clinical history of this patient that there was any defect of speech and that, therefore, these abnormal muscular slips had any abnormal effect on the movements of the larynx. It appears, therefore, that their presence did not result in any abnormality of physiological function. It is probable, as will appear from the diagram, that the slip on the posterior aspect is an aberrant portion of the posterior crico-arytenoid muscle, but it is not possible to give a simple explanation of the lateral slip. The abnormality is evidently of developmental origin, for no trace was observed of any disease or injury to the larynx such as might have caused distortion of the musculature. Moreover, in the clinical history of the case, the throat is described as perfectly normal, particular examination of this region having been made in consequence of the tuberculous condition. All the other structures met with in the dissection of the larynx were apparently normal.

The widely distributed abnormalities in this specimen are evidence of a considerable disturbance of the foetal development at some period, but no explanation is available of the course taken by the abnormal development in the case of the larynx. No previous observations were available which could serve to throw any light on these abnormalities, nor, apparently, are any anthropological data recorded which might be capable of furnishing an explanation of these structures.

THE ARTERIAL SUPPLY TO THE DUODENUM

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After having carefully injected and dissected four post-mortem specimens of the duodenum and surrounding structures I find they consistently show an arrangement of the duodenal arteries not hitherto described in textbooks of Anatomy and which I wish to report.

In all four dissections the superior and inferior pancreatico-duodenal arteries form a double chain of anastomosis along the concavity of the duodenum; one chain passing ventral to the common bile duct and the other dorsal to it.

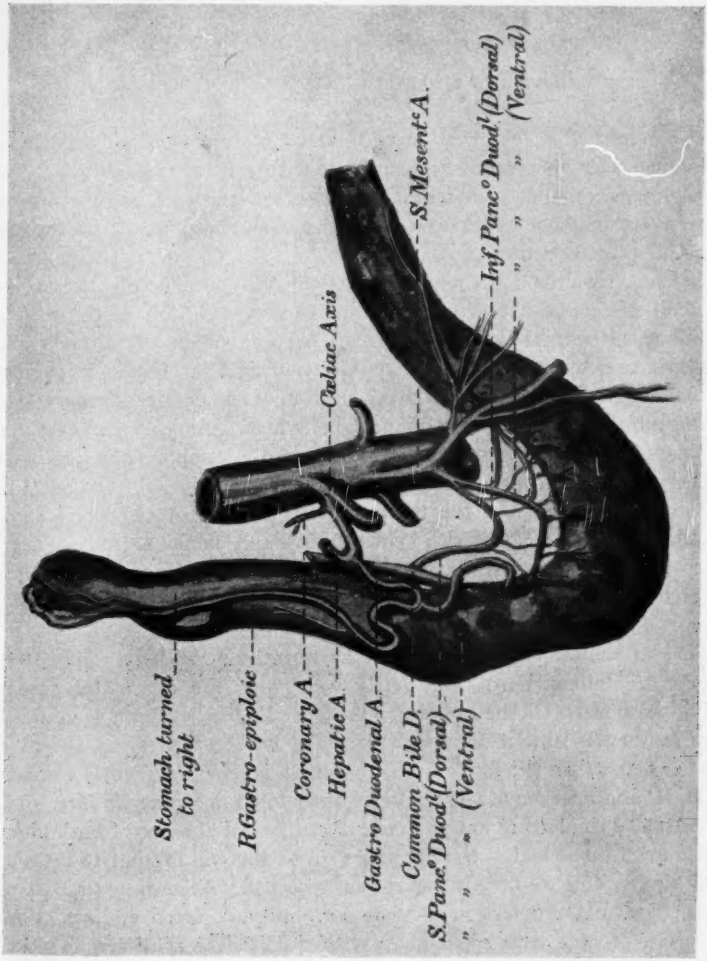
Starting from the right side the gastro-duodenal artery gives off a ventral and a dorsal superior pancreatico-duodenal branch, either before or immediately after the right gastro-epiploic artery is given off. Of these the ventral branch, which passes in front of the bile duct, is the one which is always shown in the textbooks; but the point upon which I want to insist is that there is another, quite as large, dorsal branch, hidden by the head of the pancreas and passing behind the common bile duct and the accessory pancreatic duct of Santorini, when the latter is present. These two arteries run along the concavity of the second and third parts of the duodenum, about a quarter of an inch from the gut to which they give numerous straight branches of supply.

There is nothing to show where the arcades cease to be superior pancreatico-duodenal and begin to be formed by the inferior pancreatico-duodenal; they are of the same calibre throughout their course and, for this reason, the area of supply of these arteries is of no real morphological value in determining the place at which the foregut ends and the midgut begins. The inferior pancreatico-duodenal artery comes off the back of the superior mesenteric artery while the latter is still lying behind the neck of the pancreas, about two inches above the third part of the duodenum. Since its origin lies about the same horizontal level as that of the superior pancreatico-duodenal, it hardly deserves the title of inferior save that its blood is carried to a rather lower part of the intestine. It almost at once divides into a dorsal and a ventral branch which run vertically downward behind the continuation of the superior mesenteric artery. In their passage downwards the two arteries lie about half an inch to the left of the fourth part of the duodenum and thus complete the dorsal and ventral arcades.

The arcades are specially concerned with the supply of the more dependent part of the duodenal loop; the first part and the upper half of the duodenum are supplied mainly by the right gastro-epiploic artery and do not seem to enjoy nearly so free an anastomosis as that provided by the arcades to the remainder of the duodenum.

The fourth part of the duodenum is supplied by branches which come off the left side of the superior mesenteric artery.

The practical outcome of my dissections is that surgeons must expect quite as large an artery just behind the common bile duct as there is just in



front of it, also it is noteworthy that the earlier part of the duodenum is not supplied in the same way as the succeeding parts nor have its vessels so free an anastomosis. Furthermore, it is apparent that morphologists cannot use the arterial supply to determine the limits of the fore and mid gut.

PARTIAL ABSENCE OF THE ULNA AND ASSOCIATED STRUCTURES

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It is a remarkable fact that in wide series of teratological variations the anatomical features reproduce themselves with surprising fidelity.

A given anomalous congenital condition may be comparatively rare and yet in every instance of its occurrence the same anatomical features may be almost identically reproduced.

In such cases the actual stages of the ontogeny may be obscure, nevertheless their extreme constancy seems to point very definitely to the underlying factors of the normal morphology of the parts involved. Since the recording of these cases may lead to an appreciation of the homologies of certain anatomical elements and since the recognition of any definite stereotyped form of congenital anomaly must demand an adequate embryological explanation, no excuse is needed for placing on record the full particulars of a case of a rare, but very constant, type of congenital deformity.

In a recent number of this *Journal* Jones and Roberts (3) described a case of unilateral ulnar defect, with syndactylism and partial ectrodactylism; the upper end of the radius was "over-riding" at the elbow; the carpus was represented by only three small bones, and only two metacarpal bones were present.

Several similar types of congenital deformity have been reported in the literature. Ballantyne (1) dealt fairly fully with the congenital absence of individual bones. Of the bones of the upper limb, the radius is stated to be more frequently absent than the ulna; the humerus is rarely absent as an isolated defect. In the lower limb, the fibula is more frequently absent than the tibia, and absence of the femur as an isolated deformity is rare.

In 1893 Pringle (4) reported a case of congenital absence of both ulnae.

Kummel investigated the literature up to 1896 and found 13 instances of ulnar defect and 37 of missing radius recorded. According to Ballantyne, symmetrical ulnar defect is not common, and associated malformations are less often present with ulnar than with radial defect. Mierzejewski found 23 recorded cases of congenital ulnar defect up to 1910.

Roth, writing in the *Lancet* in 1914 (5), described a deformed arm of a girl of seven years. The left arm had been "withered" since birth, but had been gradually growing more crooked. The lower two-thirds of the ulna, and three of the digits were absent. X-ray examination showed the upper end of the

radius dislocated forwards and upwards on the humerus; the shaft of the radius was very curved, with the convexity outwards. The hand consisted of a thenar and hypothenar eminence only, and the thumb and another digit. Roth assumed that the latter represented the little finger. I regard that conclusion as incorrect, and think it far more likely that the digit is the index finger and not the minimus, and that the ulnar defect is accompanied by absence of the three digits on the ulnar side of the hand. The case of Jones and Roberts above referred to is almost identical with that of Roth, and Jones described the two digits in the former case as thumb and index finger. The X-ray picture in each case indicates that the radial side of the hand and carpus is more or less complete, but that the ulnar portion is missing. In the case I report below three digits are present, and these are definitely the thumb, index and middle fingers.

Kummel (quoted by Roth (6)) classified cases of congenital ulnar defect into three groups:

(1) Ulna partly or completely absent, the radius normal though often curved, the ulnar fingers absent.

(2) Ulna partly or completely absent, the radius ankylosed with the humerus at a more or less obtuse angle. If a proximal part of the ulna is also present, it is fused with the radius and humerus.

(3) Ulna partly or completely absent, the proximal end of the radius dislocated forwards and upwards on the humerus. Mierzejewski, analysing the 23 instances he found recorded, placed 7 in the first group, 6 in the second, 7 in the third; 3 were doubtful. Of the 23 the defect was unilateral in 16 instances and right side was affected in 11 of these.

Blundell Bankart (2) has reported the case of a child of ten weeks, a twin. The right ulna was absent except for a minute portion at the elbow. The hand was slightly deflected to the ulnar side, the right elbow ankylosed. There was also a congenital contracture in the region of the shoulder, and the whole upper extremity was abducted and rotated inwards. The whole right limb was smaller than the left.

An instance of unilateral congenital malformation of the forearm came under my notice early this year. The subject was a working girl of 18 years. The right arm was affected, and no other congenital abnormality was detected. The girl was, in other respects, quite well developed. The right upper arm was slightly shorter than the left, and its muscular development was much poorer. The length of the right upper arm was $8\frac{1}{4}$ inches, the left $10\frac{3}{4}$. The right forearm was but 6 inches long, the left $10\frac{1}{2}$. The right elbow could be extended to a straight position, but could be flexed only through a range of about 60 degrees. The bony structures of the forearm were covered by a thick mass of muscle. The wrist was small, and only permitted flexion through a range of 30 degrees. The hand was deflected to the ulnar side, making an angle of about 20 degrees with the forearm. Three digits only were present: the thumb was short and thin, and the index and middle fingers were short and webbed.

X-ray examination of the right arm showed the lower extremity of the humerus to be small and the trochlear surface unduly prolonged distally. The radius was $5\frac{3}{4}$ inches long (left radius was normal and 10 inches long), bowed forwards and dislocated upwards and backwards at its proximal

Fig. 1. Case 1, showing general condition of the affected right arm.

extremity, forming a visible projection on the outer and posterior aspect of the lower arm; there was a deformed epiphysis at its lower extremity which articulated with a deformed carpus, but apparently no epiphysis at its upper end. The ulna was $2\frac{1}{2}$ inches long (left ulna normal and $10\frac{3}{4}$ inches long) and somewhat expanded at its upper extremity where it formed an unnatural articulation, a sort of ball-and-socket joint, with the rounded trochlear surface of the humerus; there was an unattached lower epiphysis just proximal to the carpus. The carpus was represented by a double row of three or four bones on the radial side, fused into an unrecognisable mass, but appearing to comprise the trapezium, trapezoid, scaphoid and a rudimentary os magnum. To the ulnar

side there was a single bone resembling a semilunar; there appeared to be a fairly normal joint between the latter, the fused bones and the distal end of the radius. The three metacarpal bones present and the corresponding phalanges appeared normal.

The family history was interesting. The girl's parents, her two brothers and her sister were all normally developed. A female cousin of her father was born with the fourth and fifth fingers of each hand "with no joints"—they were short and stiff, the defect apparently being in the phalanges. Another cousin of the father had a female child with congenital club feet, and each

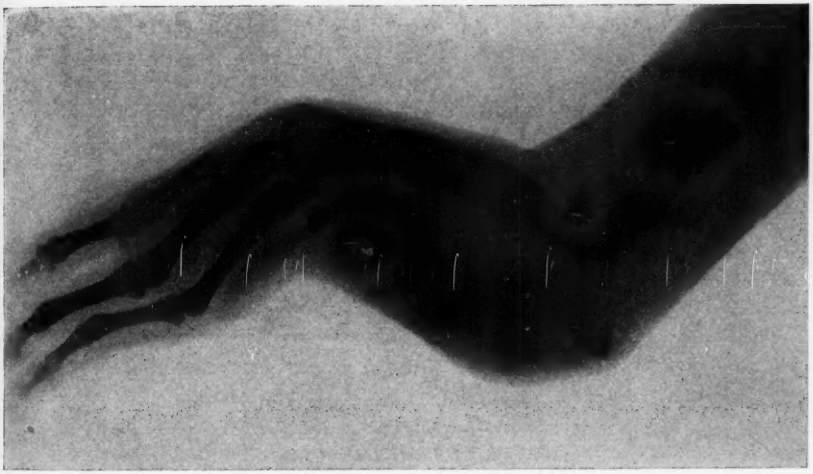

Fig. 2. Skiagram of right arm of case 1.

foot had six toes. Both of these instances occurred in the paternal grandmother's relatives. The father of the present girl had no brothers, and his only sister was stillborn. The girl's mother had five brothers and four sisters, all with no deformities, nor did the children of these exhibit any congenital defects.

In spite of the severe deformity, the girl was able to carry out her duties as a domestic servant. Writing and the finer tasks usually associated with the right hand had been undertaken by the left. Objects such as a matchbox could be picked up and held between the thumb and two fingers of the right hand, but such small objects as pins or pencils could not be so handled. The right hand was also used in the toilet of the hair. From the functional viewpoint, therefore, the deformed limb was much more useful than its anatomical condition would have led one to expect.

While preparing these notes, the writer was informed of a somewhat similar case seen by a colleague last year. The subject was a man of 25 years,

with a malformed left arm. An X-ray picture was obtained, but no detailed notes had been kept. The man had since gone into the country, and was not available for re-examination.

The X-ray picture of this case showed absence of any semblance of a joint at the elbow: the forearm was fixed in full extension, and the lower extremity of the humerus was fused with the upper ends of the radius and ulna. The

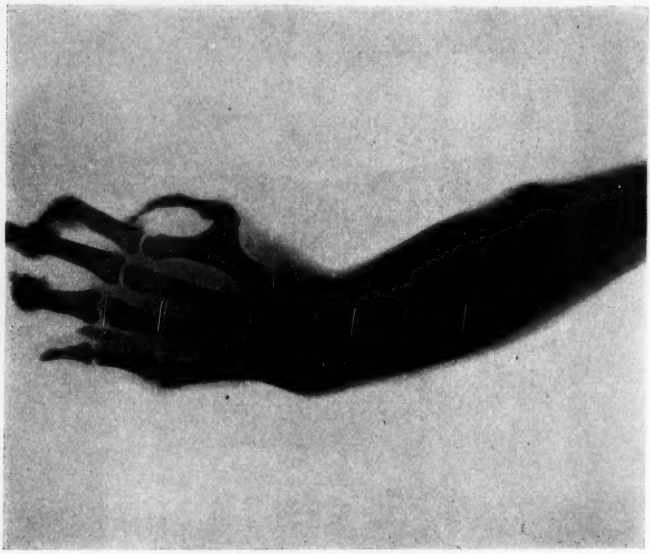

Fig. 3. Skiagram of left arm of case 2.

condition provided an example of Kummel's second group. The shaft of the radius was shorter than the normal, but its lower extremity was unaffected. The ulna was represented by a short ill-developed upper extremity, with a thin shaft about 2 inches long; but the lower two-thirds of the shaft was absent. The carpus was somewhat malformed. The fifth metacarpal bone was fused with the fourth, and to the projecting limb of this peculiar T-shaped bone the small ill-developed phalanges of the fifth finger were attached.

I am indebted to Professor F. Wood Jones, of the Anatomy School at Adelaide University, for guidance in the preparation of these notes, and to Dr H. Carew Nott, Honorary Radiologist to the Adelaide Hospital, for the X-ray work.

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UNILATERAL CRYPTORCHISM IN A RAT

By WALTER P. KENNEDY

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In the course of some investigations on certain effects of calcium diminution in the diet of rats, one of the experimental animals was found to be an unilateral cryptorchid. Notwithstanding the fact that the rat is one of the most widely used experimental animals, a careful study of the literature yielded only one previous case of spontaneous cryptorchism in this animal, namely, that described by Stone and Miles, which, however, differs somewhat from the present case. As these authors point out, the incidence of cryptorchism is relatively rare among animals in which the inguinal ring remains open throughout their lifetime, and the condition was therefore thought worthy of detailed study.

The animal was killed at the age of 193 days, having been on a calcium-poor diet from the age of 45 days, and then weighed 114 gm., that is, considerably below the average of the stock, which is about 200 gm. for this age. It was however healthy, and apparently normal in other directions. The bones were smaller and lighter than the normal of that weight, but showed no rachitic deformation. Regarding the experimental conditions, it will suffice here to recapitulate only the following details: the diet fed contained 0·088 per cent. Ca, and a liberal amount of antirachitic vitamin in the form of cod-liver oil of proved potency, and was made up as follows: purified rice starch 55 parts, caseinogen 20, oil mixture 10, salt mixture 5, ether extract of oats 5, alcohol extract of marmite 0·35, plus $\frac{1}{2}$ c.c. of concentrated orange juice *per diem*, and distilled water *quant. suff.* Further details will be found in the first paper dealing with the calcium diminution experiments (Kennedy). This diet depressed the fertility of the males exposed to it, and while they copulated freely, only a small number of matings were successful. On microscopic examination slight degeneration of the germinal epithelium was found, as is described in the case of the normally situated testis in this rat. When mated with normal females the cryptorchid rat copulated freely but on no occasion did pregnancy result.

MACROSCOPIC EXAMINATION

On opening the abdomen it was found that the right testis was ectopic, while the left had descended normally. The right inguinal ring contained the vas deferens and blood vessels but appeared to be constricted as compared

with the left, and the testis though small could not be passed through it. No testicular adhesions were found, and the organ was movable. In Stone and Miles' case the testis was firmly bound down to the abdominal wall by adhesions, and on their removal could be passed into the scrotum or abdominal cavity through the inguinal ring. The right testis was approximately one-quarter the size of that on the other side, and was closely apposed to the epididymis, which was also much smaller than its fellow. The cauda lacked the distinct vermiform appearance under the integument, but the caput did not appear to be so greatly affected, though it was unquestionably much diminished. The vas deferens was normal, and the right seminal vesicle presented a similar appearance to the left, and was distended with the usual gelatinous contents. On the left side the testis seemed normal in every way, and if allowances were made for the greater age of the animal than is usual at the particular body weight, then the organ was about ordinary size and weight. The prostate showed no pathological signs.

MICROSCOPIC EXAMINATION

The material was fixed in formol, sectioned, and stained with Heidenhain's iron haematoxylin and counterstained with thiazin.

The left testis showed a similar early stage of degeneration to testes of other males exposed to this diet. It affected some tubules but not all, and of those that were affected only the latest stages of spermatogenesis were abnormal. This is consistent with the findings of Mason who states that in progressive degenerative changes of the germinal epithelium, due to vitamin E deficiency, the advanced stages of spermatogenesis are the first to be attacked. Some tubules were normal, as can be seen in fig. 1, while in others the lumen of the tubule was filled with colloid material, sometimes exhibiting a foam-like structure (which may be an artefact); no spermatozoa were visible. In several, spermatids and granules were seen in the centre of the lumen, the latter being possibly fragmented spermatozoan heads or spermatid nuclei. They appeared to be more darkly staining and more irregular than the seminal granules which arise from the disintegration of the spermatid protoplasm during spermatogenesis. The spermatogonia, spermatocytes, and Sertoli cells exhibited a normal appearance, as was also the case with the interstitial connective cells and the cells of Leydig.

The tunica albuginea of the right testis was thickened, the tubules markedly deformed, and the germinal epithelium completely disorganised (fig. 2). No typical spermatogonia were found, but here and there lining the basement membrane were cells which might have been spermatogonia or Sertoli cells. Some of these showed mitotic figures, a few of which were tripolar. These may have been spermatogonia, while the others, which were more numerous, would be Sertoli cells. The lumen of the tubules contained foam-like colloid and cell debris. The interstitial tissue was increased in amount; not only the cells of Leydig, but to some degree the connective tissue cells also. The considerable

shrinkage which has taken place during preparation for cutting is an indication of the relatively fluid nature of the tubules, and the non-discrete condition of the germinal epithelium.

The epididymis on the left side was normal in every respect, and, as can be seen from fig. 3, the lumen of the tube contained myriads of spermatozoa. On the right side no spermatozoa were found, the lumen only containing small patches of colloid and cell debris here and there. The transverse diameter of the lumen was diminished to less than half that of the other side, and in several places in the sections of the cauda it was observed that the tube was divided into sacs by septa projecting from the lining epithelium. This is a very rare condition, and no note of it has been traced in the literature. The epithelium itself was thickened, and there was a slight increase in the amount of the intertubular connective tissue.

DISCUSSION

This case presents an example of the degeneration of the germinal epithelium of the testis retained in the abdominal cavity, probably owing to constriction of the inguinal ring. The degeneration is of high degree, and this may be ascribed to two factors, one being the diet, and the other being the temperature to which it was exposed in the abdominal cavity. In 1922, Crew advanced the idea that the reason of the aspermatic condition of the cryptorchid testis was that the higher temperature to which it was exposed in the ectopic position, as compared with that in the scrotum, constituted an unfavourable environment to such a degree as to result in degeneration. This hypothesis has been fully substantiated by the investigations of Moore and his co-workers, and by the experiments of Stone and Miles with their case of cryptorchism. The latter workers showed, by a series of measurements with a thermo-electric couple, that the skin overlying the ectopic testis (which lay between the abdominal musculature and the skin of the groin) was cooler than the skin of the adjacent abdominal wall, but warmer by 2 per cent. than the skin of the scrotum containing the normal testis.

The fact that the degeneration was more complete in this case than in that reported by Stone and Miles may be due in part to the deficiency diet, and in part to the difference in temperature, as the situation within the abdominal cavity would be warmer than that in the abdominal musculature. Moreover, in their case the testis had descended at one time, and become displaced later, while in this rat there was no evidence to show that complete descent had ever occurred, which would have offered a greater possibility of development.

Mattill and Clayton found in their experiments on the relation of vitamin E to reproduction, that deficiency of the vitamin resulted in degeneration of the testes in rats exposed to such diets, but that in several instances one testis was normal, while the other was markedly degenerated. None of these testes, however, are described as abdominal. In the series of experiments in which the present case occurred no such marked difference was observed, although

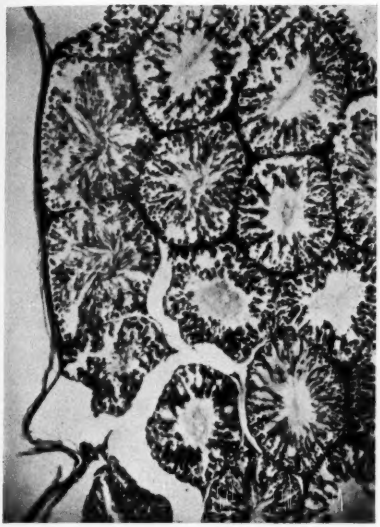

Fig. 1.

Fig. 2.

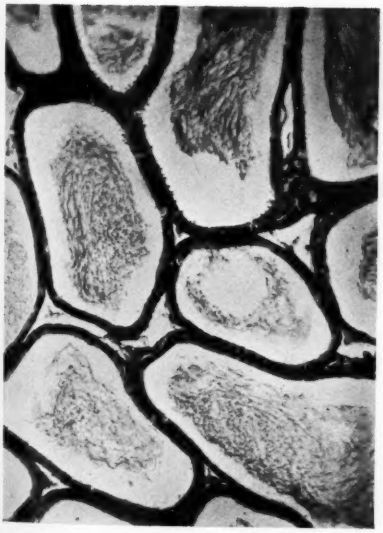

Fig. 3.

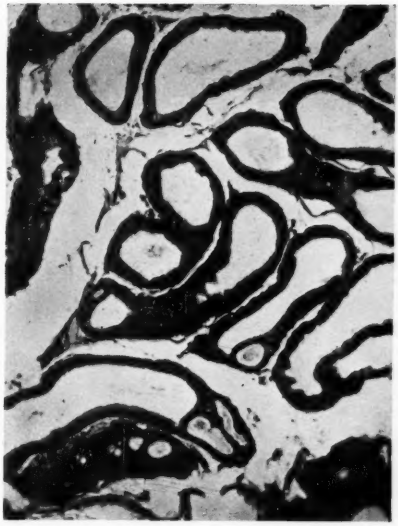

Fig. 4.

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there were slight variations and the number of animals was smaller. Under the circumstances it would seem safe to discount this as a possible explanation, since the temperature difference in itself is adequate to cause the condition.

SUMMARY

A case of spontaneous cryptorchism in the rat is described, and the cause of the ectopic situation is suggested to be a developmental failure of the organ to pass into the scrotum owing to a constriction of the inguinal ring.

This research was conducted under the tenure of a grant from the Medical Research Council.

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DESCRIPTION OF FIGURES

Fig. 1. Left testis, scrotal, showing normal tubules, and some with slight degenerative changes. The intertubular tissue has taken up the stain very deeply. Tunica normal. The space in the left-hand lower corner is an artefact. × 90.

Fig. 2. Right testis, abdominal, showing advanced degeneration of the germinal epithelium, slight increase of interstitial elements, and marked thickening of the tunica albuginea. × 90.

Fig. 3. Left epididymis, normal, lumen filled with spermatozoa. × 90.

Fig. 4. Right epididymis, lumen diminished in size, and containing only traces of colloid or cell debris; slight increase of intertubular connective tissue. Several of the cross-sections show a sacculated condition. × 90.

NOTE ON DR HUNTER'S PAPER ON DEVELOPMENT OF THE DUODENUM

By Professor J. ERNEST FRAZER
London

In the January number of this *Journal* Dr R. H. Hunter has a paper entitled, "A contribution to the development of the duodenum," in which he criticises certain opinions advanced by me some years ago. It is hardly necessary for me to say that I cannot possibly, and do not wish to object to anyone holding opinions contrary to those that are mentioned, but as the reasons brought forward against them are, I think, weak and inadequate, and as, moreover, some of the presentations are misleading, I may be considered justified in calling Dr Hunter's attention to some of these points.

So far as concerns his general account of intra-abdominal happenings in the stages with which he deals, I have little to say: as might be expected, Dr Hunter's description is essentially in agreement with what was written by me on this matter several years ago. There is one point, however, which seems to call for some notice, inasmuch as some stress is laid by him on its bearing on the formation of the duodenal curve. I refer to the presence of those condensations which he terms "fixation bands," and which are suggested as affording fixation for the ends of the duodenum, allowing the loop to form between them. He rightly says that Robbins and I (when dealing with the larger question of intestinal rotation) stated that we could not find "undoubted evidence" of the band of Treitz earlier than our 35 mm. stage, and then proceeds to speak of his bands of condensation being found much earlier than this. I may say at once that we were well acquainted with these condensations about the vessels, but we took for our standard of "undoubted evidence" the presence of some continuity or direct connection with the coats of the duodenal wall, and our statement was the result of our examination. Enthused by Dr Hunter's assertions, I have re-examined some of my embryos on this point, but, with the exception of some indefinite indications at 30 mm., I can only repeat the original statement as satisfying the original standard. I do not know what standard Dr Hunter adopted to test the value of his bands, but I can see no reason at present to alter that which we had. I may add that, seeing how early and definite is the occurrence of our "retention band" lower down, I had confidently expected to find some sign of a band of Treitz at 22 mm. or before this, when the duodenal curve was beginning to show itself, and had been surprised and disappointed when I failed to come across it definitely.

It is with another matter altogether, however, that I am particularly concerned. I refer to Dr Hunter's rejection of my view that the duodenal loop is intimately associated in its formation with the head of the pancreas—because I think he has put a mistaken value on the reasons he brings forward against it. These are, shortly, the argument from abnormal conditions and from comparative anatomical data. I need hardly say that these were present in my mind when I came to the conclusions with which he finds fault, but as possible objections they seemed to me, for reasons which will become evident, of little worth in face of the actual facts observed.

It is as well to be quite clear, in the first place, about the subject under discussion. I was describing the method of production of the *normal* duodenal loop, such as we see every day, and this loop I stated (in my opinion) to be curved out by the growth of the head of the pancreas in the mesoduodenum. The abnormal loop does not come into the question at all, for it is not a normal loop. I do not think I ever implied, and I certainly never meant to say, that any looped arrangement of the tube must own the pancreas as an immediate cause, but only the normal loop of ordinary descriptions. On the contrary, I recognised the fact that the duodenum and mesoduodenum increase in length and size respectively, ahead of and apart from the pancreatic growth: this increase, to which I called attention particularly where it affected the lower part of the mesoduodenum, is seemingly in anticipation of that of the pancreatic head, and is comparable with what one sees in various parts of the body where mesodermal beds are formed in anticipation of subsequent invasion by ingrowths from other layers. The weakness of the argument from abnormalities under these circumstances may perhaps be rendered more evident by taking a parallel case as an illustration. The general shape of the normal scrotum in a normal man is conditioned by the presence within it of the two testes, and varies with their size, shape, etc. Yet the scrotum is formed before the testes reach it, and is so far independent of them. But if we take a man in whom both of the glands are retained, the scrotum is still there, but its form is not conditioned by the testes. Are we justified therefore in saying that the outer form of the normal scrotum does not depend on its contents, that it is not curved out by these, because of the abnormal conditions in the double cryptorchid? To ask the question is to exhibit the weakness of the reason and the futility of the argument from it. In a similar way the view that the duodenum is curved out in its normal loop by the head of the pancreas does not seem to be affected in the least by the existence of an abnormal loop in which the pancreas is not contained: on the contrary, the abnormality in some ways seems to support the suggested conditions of normality, for the presence of an abnormal loop postulates growth of duodenum and mesoduodenum, and the latter is not occupied or only partly occupied by the pancreas, whereas in every case in which the gland occupies the mesoduodenum to the full the loop is "normal." This is applicable to cases such as Gordon Taylor's, or those others to which Dr Hunter refers, but the interesting

condition described by Reid comes under a different heading. In this case, however, there seemed to have been a total absence of any attempt at rotation of the gut of the umbilical loop, and hence of any chance of the lower portion of the duodenum coming into place. One may theorise to a great extent on this case, but one can actually be sure of very little. It seems to me that there is good evidence that the pancreas did its best under the trying circumstances of this case, but the whole thing is so very doubtful, so far as the possible actions of the various factors involved are concerned, that its evidential value will, I think, have to remain undecided.

The argument from comparative anatomical data, also, does not seem to come into the matter—at least, without further knowledge of the conditions. It would appear, judging from the results reached, that the conditions under which they are attained in most animals must differ from those obtaining in man. It was this general consideration that Dr Robbins and I had in mind when we put "in Man" as a qualification to the title of our paper on intestinal rotation; whether the distinction was of real value or not was of little importance, for we only worked on human embryos. The mere presence of a duodenal loop signifies only growth of the tube and of the mesoduodenum, if we can apply what has already been said about the human embryo, but in this case the shaping of the loop into the "normal" depends (as I hold) on the presence of the head of the pancreas within it, wherefore, arguing still from the human side, it is only those animals normally having a pancreas included in the loop which can be compared for purposes of argument with the human subject. It is so many years since I dissected a cat, that my memory of its duodenum is more than vague, but Mivart speaks of this as describing "a rather wide curve, which embraces the pancreas and receives its duct....It lies on the right side of the abdomen." Dealing with the pancreas he says, "the larger part, the head, passes backwards along the convex margin of the duodenum." All this is quite as one might expect, and in keeping with the view I put forward, but I cannot claim it in support, for I consider that the development of none of these other forms can be used as valid arguments *pro* or *con* until more is known of the conditions under which the duodenum takes shape. I know of one form at least which has been worked out (*Trichosurus vulp.*) with regard to associated matters, and in that case (*Phil. Trans.* vol. v, p. 208) the author, Miss Tribe, did not consider that my conception of the agency at work was applicable. This seemed to me to be a perfectly reasonable opinion, having regard to the conditions, and the case provides a good example of the difficulty that must exist in applying the findings in one animal to another of a totally different kind.

The third reason adduced by Dr Hunter to justify his want of belief in the moulding force of the pancreas is to the effect that, at a period when the duodenal loop is well developed, the pancreas is a relatively unformed structure lying more or less diffusely in the mesentery. Dr Hunter will pardon me, I hope, if I say that this statement is misleading. The duodenal loop is not

well developed at the 22 mm. stage, as can be seen from his own figure of a reconstruction: it is indicated, in an incomplete way, lying altogether to the right of the median mesentery, and he would soon discover how little of the curved tube deserves the name of duodenum if he would work out the vascular distribution. Moreover, the pancreas, as can be seen from his own figure of a section, is a fairly prominent, if diffuse, content of the mesoduodenum; it seems to show in Dr Hunter's reconstruction, although it is not labelled, occupying the upper rounded curve of this part of the gut. Everybody who is accustomed to examining sections of embryos has noticed that the physical effects of any structure are transmitted for a considerable distance through the surrounding layers, so that a small mass of any sort will produce an elevation on some free surface a considerable distance away, and, to my mind, the amount of pancreatic growth in the mesoduodenum at this stage is more than sufficient to cause a prominence of mesoduodenum and duodenum to the right, as it is to make the first become convex to the left: this latter effect, by the way, is visible in Dr Hunter's section.

It is unnecessary to labour these points further, and we can turn to see how the author accounts for the duodenal curve. With his first conclusion one can have no quarrel, but something must be said about the second. Here he assigns the adult position of the duodenum to three factors acting during development. The first factor is a series of developmental growth changes leading to the formation of two loops in the primitively straight tube. If, for brevity, we let this pass, we come to the second factor, which makes the position of these loops governed by changes in the neighbouring organs forcing the tube to take the form shown in the various stages: no further light is thrown on the way in which this rather vague statement is to be understood, and I must find myself in agreement with it, because I hold that the head of the pancreas is the particular neighbouring organ concerned, the only one in which change is conformable with the shape of the curve, and the only one except the liver in relation with the duodenum—I am not, of course, including the effect of growth of the stomach on the position and direction of the upper part of the tube, a matter on which we both seem to be more or less in accord. Dr Hunter does not specify any particular organ as implicated in his second factor, so the pancreas remains in possession at least by default. The third factor does not come into the discussion, and his third conclusion, relegating the pancreas to a rôle of growth along planes of least resistance, to be moulded by neighbouring organs rather than to mould them, is an expression of a pious belief which seems to me to be not only lacking in support from anything he has said, but to be even opposed to what can be gathered by unbiassed examination of sections of embryos of various stages.

A CASE OF HYDROCEPHALUS IN AN INFANT, WITH COMMENTS ON THE SECRETION, CIRCULATION AND ABSORPTION OF THE CEREBRO-SPINAL FLUID

By R. J. GLADSTONE, M.D., F.R.C.S., F.R.S.E.

AND

H. A. DUNLOP, M.R.C.S., L.R.C.P.

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CLINICAL HISTORY

The specimen which we shall now describe, and which has led us to the study of the pathological changes associated with congenital hydrocephalus in general, was the brain from a boy aged 2¼ years, who was under the care of Dr Hildred Carlill and Mr E. Rock Carling at Westminster Hospital. The post-mortem examination was conducted by Dr J. Braxton Hicks to whose kindness we are indebted for the opportunity of reporting the condition of the brain.

The child had been brought up by foster-parents. When adopted he was 13 days old and seemed to his foster-parents to be a "normal baby"; as he grew older, however, both parents noticed that he was unnatural and "did not grow properly," neither did he learn to walk or talk. He cried continually. The only evidence that he could see was that he flinched when placed in the sunlight.

FAMILY HISTORY

The child was illegitimate. There were three older children of the same mother but different father; these were quite healthy. Both the father and the mother of the boy were also said to be quite healthy. Seven of the mother's sisters and brothers went blind when they were about 21 years of age[1]. All other members of their family were quite normal.

[1] This was most probably due to the disease known as Hereditary Optic Neuritis (hereditary optic atrophy or Leber's disease). Descent is said to be generally through an unaffected female to the males. There is a central scotoma, which may be either partial, for colours only, or complete for white also. Certain cases of optic neuritis, not necessarily hereditary, are associated with hydrocephalus and we wish to draw attention to those remarkable cases described by Nettleship, Priestley Smith, Leber, Emrys Jones and others, in which optic neuritis is associated with persistent dripping of watery fluid from the nostril, the symptoms being those of increased intracranial pressure, and a high degree of amblyopia due to papillitis followed by atrophy (Swanzy and Werner, *Diseases of the Eye*, 13th ed., p. 380).

PREGNANCY

The baby was born at term; the labour was difficult; no instruments were used.

CONDITION ON ADMISSION TO HOSPITAL

There was a bulging of the skull on the left side, with flattening on the right. No other deformities were observed.

The child was much wasted and appeared to be nearly blind, the left eye being apparently worse than the right. The commonest position of the eyes was one of convergence, but there were frequent rapid lateral movements. Both pupils reacted sluggishly to light, the contraction of the left being specially feeble. There was marked atrophy of the optic discs; the appearances did not indicate whether this was primary or consecutive.

There was general spasticity of the muscles. The elbows were firmly flexed. On placing the child on his feet there was a tendency towards the position characteristic of scissor-gait, but he could not walk or stand unsupported. The head fell back helplessly on the shoulders. The tendon reflexes were exaggerated; the epigastric and abdominal reflexes were absent, while the plantar response was extensor on each side.

The temperature and pulse were noted as normal; likewise the urine. The Wassermann reaction in the blood was negative. The cerebro-spinal fluid was found to have a normal pressure, and it showed no pathological change when examined by the usual methods, including the complement-fixation test.

SUBSEQUENT HISTORY

After the child had been a month in hospital a distinct improvement was observed. He cried less, and smiled occasionally, sometimes on being spoken to. He did not move his arms at this time, but often kicked his legs about. He had apparently, however, incontinence of both urine and faeces.

After another month, decompression was performed in the right parietal region. The meninges were oedematous. No cyst was detected.

Death occurred from shock two hours after the operation.

DESCRIPTION OF BRAIN

The brain, fig. 1, which had been divided into two halves at the post-mortem examination, measured 13·5 cm. in length. It showed a great enlargement of the cavities of both lateral ventricles, which affected chiefly the body, and posterior cornu. The antero-posterior diameter of the left lateral ventricle was 90 mm. and its greatest vertical diameter 43 mm. The choroid plexuses of the lateral ventricles appeared normal in size, but they were tough and fibrous in consistence. The central part of the corpus callosum appeared as a thin membrane, which, owing to the distension of the lateral and third ventricles was torn away from the fornix, and arched upwards to a distance of

3 cm. above the level of the optic thalami. The curve of the attenuated genu was widened out, and in its concavity were attached some remnants of the septum lucidum. The rostrum was continuous with the lamina terminalis, which contained an anterior commissure of normal size, behind which the anterior pillar of the fornix could be seen sinking into the lateral wall of the third ventricle. Behind, the thinned-out splenium of the corpus callosum was connected with the posterior part of the body of the fornix. This was torn away from the anterior pillars. In the upper part of the wall of the left lateral ventricle there was a small aperture which appeared to be closed by a thin

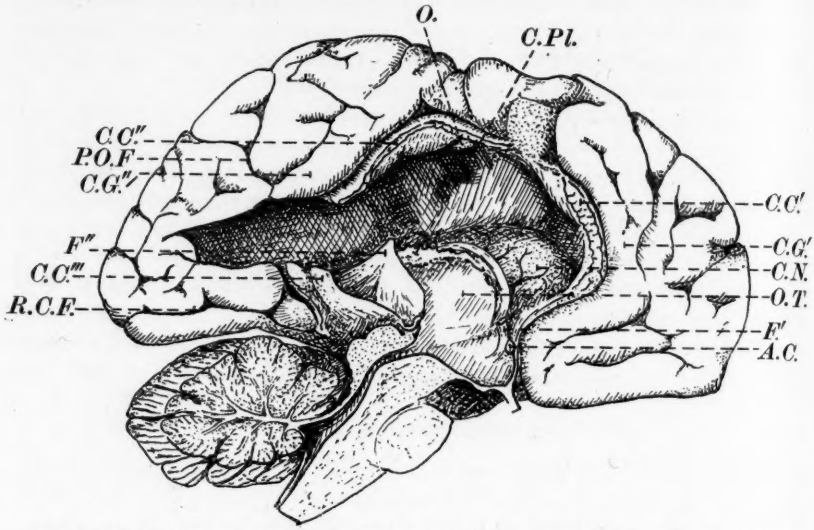


Fig. 1. Left half of the brain showing distension of the lateral ventricle, attenuation of the corpus callosum and rupture of the fornix. *A.C.*, Anterior commissure. *C.C.'*, *C.C.''*, *C.C.'''*, Corpus callosum. *C.G.'*, *C.G.''*, Callosal gyrus. *C.N.*, Caudate nucleus. *C.Pl.*, Choroid plexus. *F.'*, *F.''*, Fornix. *O.*, Opening in roof of lateral ventricle. *O.T.*, Optic thalamus. *P.O.F.*, Parieto-occipital fissure. *R.C.F.*, Retro-calcarine fissure.

covering of pia mater presumably lined by ependyma, fig. 1, *O.* A similar thinning-out of the wall of the lateral ventricle was present on the right side.

On examining the convolutions on the lateral surfaces of the brain, a deep fissure was seen coursing upward and slightly backward from the stem of the fissure of Sylvius, to the supero-mesial border, in the position usually occupied by the central fissure of Rolando. On the right side, fig. 2, this fissure was uninterrupted. On the left side, however, fig. 3, there was a bridge separating the main fissure into an upper part, which apparently represented the central fissure, and a lower which corresponded to the stem and part of the posterior horizontal limb of the lateral fissure. This, with the upper part

of the sulcus, ran a much more vertical course than is normal, owing to the expansion of the occipital and parieto-temporal regions of the brain, around the enlarged posterior horn and body of the lateral ventricle. On the right side the two fissures were continuous, and neither pre-central nor post-central

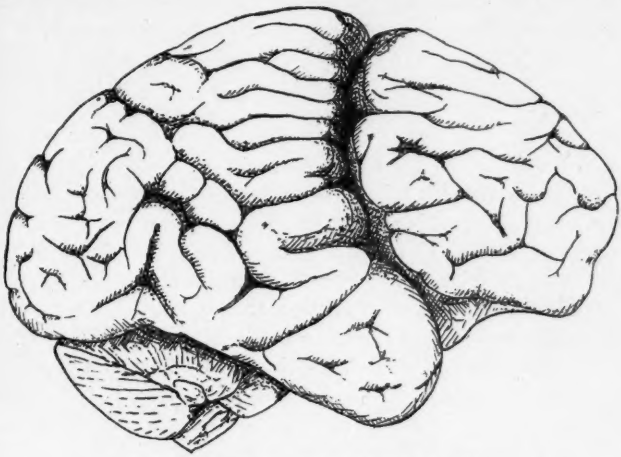


Fig. 2. Lateral aspect of right half of brain.

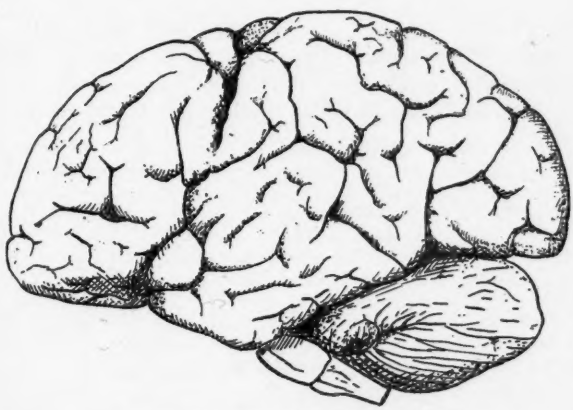


Fig. 3. Lateral aspect of left half of brain.

fissures could be distinguished; moreover, the arrangement of the convolutions and fissures was for the most part horizontal, and the cortex of this side exhibited a high degree of folding.

On the medial surface, the callosal or cingular gyrus was easily recognised, and was seen to be interrupted in its central part, where the corpus callosum

was bulged upwards towards the supero-mesial border of the hemisphere, at the point where this was cut by what appeared to be the central fissure, fig. 1. The internal parieto-occipital fissure rose more vertically than normal and formed nearly a right angle with the calcarine fissure.

The third ventricle and the aqueduct of Sylvius were slightly enlarged, but the fourth ventricle and the surrounding parts appeared normal.

Microscopic appearances of the choroid plexuses, septum, lucidum, ependyma and nerve tissues.

Serial sections of these parts were cut, and stained with (1) haematoxylin and eosin; (2) van Gieson's acid fuchsin stain; (3) picro-indigo-carmine; and (4) Weigert's stain for elastic tissue. Similar sections were cut for comparison from the brain of a child who died aged one year and two months. The cause of death was leukaemia, but except for the presence of a large excess of lymphocytes in the blood, the brain appeared normal[1].

The choroid plexuses from the lateral ventricles of the hydrocephalic brain were much thickened, and the ependymal secretory cells covering the plexuses were swollen. The average diameter of 50 of these cells in the hydrocephalic specimen was 12·7 μ; in the control 9·16 μ. There was, moreover, a considerable degree of proliferation of the ependymal cells, which, instead of forming a single layer on the surface, were irregularly massed, and in some places shed off into the spaces between the villi. On examining the minute structure of the cells, the cytoplasm in the hydrocephalic specimen was seen to be more opaque and more diffusely stained than that of the control, while the nuclei were less deeply stained and the nuclear membrane less defined. The chromatic material was also less sharply outlined, and the nucleolus less distinct. Furthermore, the nucleus appeared to be more central in the rounded swollen cells of the hydrocephalic case, while it was nearer the basement membrane in the control. In the abnormal specimen there is a considerable increase in the amount and density of the connective tissue which forms the central core of each villus. In many places the connective tissue is infiltrated with small round cells, and in some parts the tissue spaces appear to be filled by a fibrinous exudate. The walls of the small vessels, both arterioles and venules, are greatly thickened. The thickening appears to involve all three coats of the vessel wall. In some cases, fig. 4, *A*, there is a hyperplasia of the intima, with hypertrophy of the individual endothelial cells which are swollen up and rounded, and in some vessels, especially the larger, are shed off into the lumen.

In the sections stained by Weigert's method, it is also noticeable that there is a thickening, which is chiefly fibrous in nature, external to the fenestrated membrane of Henle. Beyond the thickened adventitia there is an accumulation of cells with round and oval nuclei. These are larger than lymphocytes, their

[1] The authors wish to express their thanks to Dr D. N. Nabarro for his kindness in supplying them with this brain for use as a control specimen.

outlines are indistinct and they appear to have arisen as a proliferation of the tissue cells.

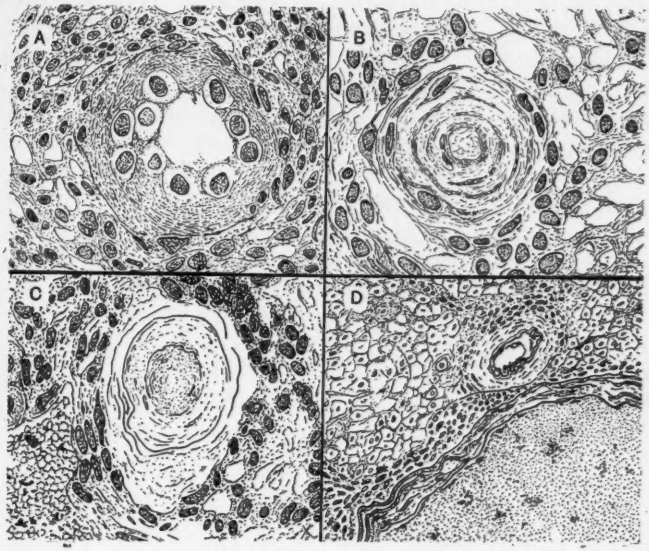


Fig. 4. *A*, Transverse section through a small arteriole of the choroid plexus, highly magnified. Stained with haematoxylin and eosin. It shows marked degenerative changes. The endothelial cells are swollen up and rounded; their nuclei, which are poorly stained with the basic dye, are finely granular. There is no distinction between subendothelial layer and internal elastic lamina, the endothelial cells being imbedded in, and surrounded by, a finely granular wax-like material faintly stained with eosin. This was enclosed in a concentrically arranged zone of cells which represented the degenerated muscular and fibrous tunics of the artery, and which passed insensibly into the surrounding connective tissue.

B, Section through one of the larger corpora amylacea in the choroid plexus of the lateral ventricle. It shows a clear central zone brightly stained with eosin, surrounded by concentric laminae of a hyaline material also stained with eosin; these alternate with layers containing what appear to be flattened and degenerated nuclei. Diameter 45 μ.

C, Section through a large corpus amylaceum, with what appears to be a calcareous nodule in the centre. The concentric laminae containing traces of degenerated nuclei, seen in the preceding specimen, have almost disappeared. Diameter 50 μ.

D, Section passing through a vein of the choroid plexus a small part of which is shown in the illustration. It is completely filled with a coagulum, consisting of broken-down blood corpuscles, and a fibrinous material containing amorphous granules. A small arteriole, with shed, degenerated endothelium, and thickened wall lies above the venule. Both vessels are surrounded by areolar connective tissue which appears to be undergoing fibrous degenerative changes.

Many of the venules are greatly distended, and completely filled with a coagulum, which appears to consist of broken-down blood corpuscles, and amorphous granules scattered through a fibrinous basis, fig. 4, ***D***. Whether this clot was formed during life or post-mortem it is difficult to determine.

We are, however, inclined to the view that it was probably post-mortem in formation, and therefore could not have caused obstruction during life to the return of venous blood from the plexuses. Moreover, such extensive thrombosis would lead, in our view, to such stagnation of the choroidal blood flow that further secretion would be prevented. Ligation of the vein of Galen, i.e. sudden obstruction, leads to hydrocephalus in only a certain number of cases. Nevertheless, gradual, or more probably, partial, obstruction to the venous outflow, as by compression of the vena Galeni by a cerebral tumour, is a well-recognised cause of hydrocephalus. Distension of the ventricles brought about in this way by excessive formation of fluid is usually referred to as *productive* hydrocephalus, in contradistinction to *obstructive* hydrocephalus. Into the category of productive hydrocephalus falls the *acute ependymitis serosa* of Quincke, in which also the cerebro-spinal fluid is practically of normal composition. Reference will be made later to cases of productive hydrocephalus associated with inflammatory changes of a more chronic nature in the plexus. Well-marked evidences of chronic inflammation, in the form of infiltration with round cells and tissue proliferation were present in the specimen described here, which probably, therefore, is to be regarded as an example of hydrocephalus of the productive or choroidal type. In this case, also, changes in the vessel walls were present, which would account for extensive thrombosis occurring soon after or immediately before death. There was no evidence of obstruction of the foramina of Magendie and Luschka.

In addition to the changes described above, the bodies known as corpora amylacea, fig. 4, *B* and *C*, and fig. 5, were present in the choroid plexuses, in the sub-ependymal tissue of the ventricles, on the upper surface of the corpus callosum immediately beneath the pia mater, and in the nerve substance, e.g. in the cerebral hemispheres, corpus callosum and septum lucidum. As the presence of these bodies in the specimen under consideration must be regarded as an abnormal, and probably morbid, condition, and also, as their presence is of significance from the etiological standpoint, it will be necessary to describe them in some detail. Their occurrence in this case, in a child of $2\frac{1}{4}$ years, is so far as we have been able to ascertain the earliest age at which their presence has been recorded. In the classical work by Stürmer on these bodies a case described by Tuczeck of a girl aged 9 is cited as the earliest age at which they had been found. This girl died with symptoms of chronic poisoning by ergot. During the illness which preceded her decease she suffered from "epileptic cramps," nervous irritability and stupor. There was complete absence of the knee jerks. Death took place during coma. At the post-mortem examination there was found pachymeningitis externa; dilatation with thickening of the walls of the vessels of the cerebral cortex; degeneration of the posterior columns, throughout the whole length of the spinal cord; purulent bronchitis, and tuberculosis of the liver, kidneys and other organs. A fairly large number of corpora amylacea was present in the degenerated parts of the posterior columns. These showed a well-defined concentric lamination.

In the brain of the leukaemic child alluded to above, which we have employed as a control specimen, careful search failed to reveal the presence of corpora amylacea, in either the brain substance, the sub-pial or sub-ependymal tissue.

It is generally believed that their occurrence indicates a degenerative or inflammatory change in those parts of the nervous system in which they are found, and their presence in the brain of the hydrocephalic case we are considering, and in Tuczeck's case, quoted above, may be regarded as corroborative evidence in support of this belief. In both cases signs of chronic

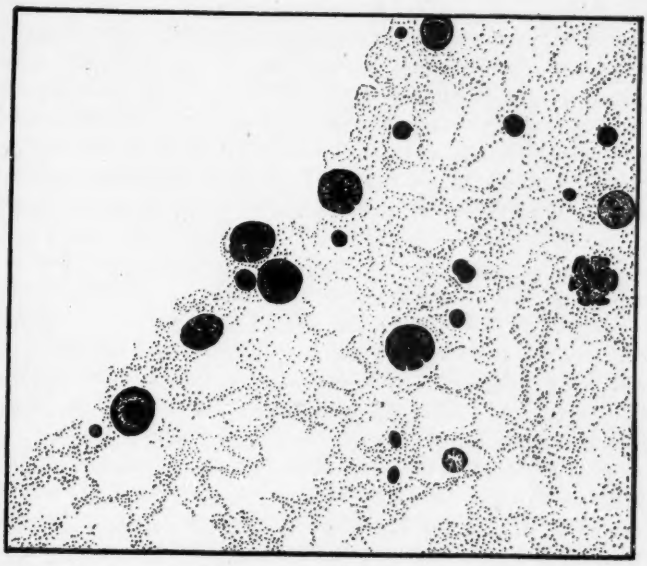


Fig. 5. Corpora amylacea situated in the sub-pial tissue above the corpus callosum and at the bottom of the great longitudinal fissure—from the case of hydrocephalus. They measured from 2·5–10 μ in diameter. Concentric lamination, radial fissuration, and deeply stained oval or spherical masses lying within the bodies were observed in the larger corpora amylacea.

inflammation and degeneration were present in the tissues and membranes of the central nervous system; and the formation of corpora amylacea, in children of so young an age, may be considered as dependent on one or both of these changes. Moreover, their presence in the case of hydrocephalus, may be taken as evidence that the tissue changes described above were the result of disease, rather than a congenital or germinal defect of development.

The most complete description of corpora amylacea with which we are acquainted is that of Rudolf Stürmer (29). This author describes these bodies

as "small spherules averaging in general 10–20μ in diameter, but with extremes varying from 3–50μ. Under the microscope they appear in the unstained condition as round or oval colourless bodies, which are either quite transparent, or have the appearance of ground-glass. They have a high refractive index. Their circumference in fresh preparations is more or less sharply defined. They are often surrounded by a narrow border of more highly refractile myelin-like substance. In fixed preparations their surface is often uneven, granular or notched, figs. 4 and 5, this condition being an artefact. A concentric lamination is usually seen in the corpora amylacea. The concentric appearance is beautifully seen in unfixed specimens stained with neutral red. There is often, however, only a rough distinction into two parts, viz. a laminated central portion of varying diameter and a marginal part constituting an outer shell. In the centre of the concentric structure, fine particles are found, which give the impression of their being 'nuclei of crystallisation.' Very fine radial striation is sometimes seen in the centre of the bodies. Radial striation is, however, not a general character." Stürmer also discusses the distinctive characters of these bodies as compared with concentrically laminated structures occurring elsewhere, such as biliary, vesical and renal calculi, and with calcareous concretions found in the membranes of the brain and spinal cord, lungs, prostate gland and other organs. Further, he considers the microchemistry of the corpora amylacea of the central nervous system especially in relationship to the amyloid substance of lardaceous disease, and has come to the conclusion that no definite relationship exists between them. As there appears to be a considerable looseness in the use of the terms which have been applied to the various concretions, concrements and deposits which are found in the central nervous system and elsewhere, we consider it necessary to allude here to the distinctions which have been drawn by Siegert between two principal types of colloid bodies.

According to this author, under the general term *corpora colloidea*, there may be distinguished:

A. *Corpora versicolorata.*

1. They are well stained by the halogen group of elements (chlorine, bromine, iodine). They moreover show the reaction of amyloids to different aniline stains.
2. They are brittle or friable in consistence.
3. They possess a characteristic form and structure.

   Thus they are:

   (*a*) spherical, oval or multangular with rounded angles;

   (*b*) concentrically laminated;

   (*c*) in some cases radially streaked.
4. They never originate by direct transformation of cells.
5. They never calcify.

The corpora versicolorata include:

(1) The corpora amylacea of the central nervous system.

(2) The structures discovered by Friedreich in the lungs.
(3) Some of the prostatic concrements.
(4) The corpora amyloidea found in the mucous membrane of the urinary passages.

B. *Corpora flava.*

1. These are not brightly stained by the halogens. By iodine they are coloured yellow like the surrounding tissues. Moreover, they show the reaction of the "hyalins" to acid-containing stains.
2. They are wax-like in consistence.
3. They vary greatly in form:
   (*a*) sometimes regularly spherical, sometimes quite irregularly formed;
   (*b*) the concentric lamination may be absent;
   (*c*) they are never radially streaked.
4. They originate by direct transformation of cells.
5. They are frequently calcified.

The corpora flava include:

(1) The corpora arenacea (brain sand) of the central nervous system.
(2) The structures discovered by Langhans in a carcinoma of the lung, as well as the analogous structures described by other authors.
(3) The psammoma granules of Virchow and others.
(4) Some of the prostatic concrements.

It will be noted that according to Siegert the corpora versicolorata, among which the corpora amylacea are included, never calcify. The choroid plexuses of the hydrocephalic brain which we have described, and those of adult brains, both with and without hydrocephalus however contained bodies which have all the characters of the corpora amylacea described by Siegert, and also contain numerous large concentrically laminated and calcified bodies which are undoubtedly corpora arenacea or brain sand, and there appear to be bodies which are intermediate in character suggesting that with increase in the size and age of the bodies, changes in structure and chemical constitution take place, which may be responsible for the diversity of opinion which exists as to their separate nature and origin. With respect to the origin of these structures Stürmer summarises the various hypotheses put forward by different authors under the following headings:

1. The *gliogenic theory*, which supposes them to have arisen from the glia cells, including their nuclei.

2. The *neurogenic theory*, which postulates that they originate from the nerve elements, and more particularly, from the axis cylinders or myelin sheaths of the nerve fibres, or from both of these.

3. The *lymphogenic theory*.

4. The *haemogenic theory*.

5. Origin as the result of *chemical changes in the fluid contained in the tissue spaces*; either with or without participation of the myelin.

In criticising these different theories as to the origin of the corpora amylacea,

Stürmer has conclusively shown that the true corpora amylacea do not arise as a structural product of either the glia, or nerve elements alone, or from the lymph or blood, but that they arise only as a general pathological metabolic product of the tissues of the central nervous system as a whole. Their close relation to the glial tissue, and to the vessels of the pia mater and of the brain and cord, is explained by this tissue acting as a filter or net which entangles the bodies in its meshes, and prevents their being washed away into the blood-stream. The absence of the corpora amylacea in the new-born child, and the almost constant appearance of these bodies in individuals over 30 years of age, and, further, their presence in large numbers in older persons indicates their origin as a degenerative metabolic product of the nerve tissues as a whole. The waste products of the tissue metabolism contained in the tissue fluids of the central nervous system are deposited both in the tissue, and in the spaces of the tissue.

The occasional absence, or very sparse appearance of corpora amylacea in old subjects of 70 years and upwards, is in favour of the view that their presence, although almost constant in individuals over 30 years of age must not be regarded as the normal condition of the healthy adult, or even a purely senile manifestation, but that they are associated with an altered metabolism, and the morbid formation of waste products in the central nervous system. When present in large numbers in young subjects there is usually evidence of a degeneration or chronic inflammation of the parts in which they are situated. Applying these considerations to the case which we have described, we consider that the presence of the corpora amylacea in the choroid plexuses and other parts of the brain in a child so young may be taken as evidence of chronic disorder probably of an inflammatory nature, and that the condition of hydrocephalus and other changes in the brain are not due to a primary so-called germinal defect in the development of the embryo, but to intra-uterine disease, which may have affected the chorion and placenta and thus interfered with the proper nutrition of the embryo, and prevented the normal development of the brain.

The conclusions which may be drawn from the study of this and similar cases, and more especially from a consideration of the condition of the choroid plexuses and ventricular ependyma, appear to have an important bearing on the etiology of hydrocephalus in general.

In the first place we wish to draw attention to the meaning of the term "congenital" as commonly applied in the description of hydrocephalus. It is apparently used to denote a form of hydrocephalus which is non-inflammatory in origin, and due to some germinal defect in development. A considerable proportion of cases of hydrocephalus which are included in this category, however, appear to be the result of pre-natal disorders which may be either inflammatory, or due to defective nutrition of the growing embryo. These factors apparently act by causing an alteration in the normal balance of secretion and absorption of the cerebro-spinal fluid; and also by producing

morbid changes in the cerebral vessels which interfere with the normal circulation of the blood. These morbid changes affecting the vessel walls are not confined to the choroidal and other cerebral vessels, but affect the vessels of the embryo generally, and of the chorion, as is evidenced by the frequency with which these cases are accompanied by hydramnios, oedema of the foetal tissues, and effusions of fluid into the pleural, pericardial and peritoneal cavities.

Secondly, we wish to draw attention to the occasional presence of thrombosis in the veins of the choroid plexuses. This we regard as secondary to the disease of the vessel walls, and may be an accessory factor in the production of the hydrocephalus. It is conceivable that obstruction may act mechanically by causing an increased filtration of cerebro-spinal fluid, and also, as a result of stasis, by producing a local increase in the carbonic acid content of the blood, it might stimulate an increased secretion of this fluid. It is possible also that a serous transudation may take place, which is comparable to the formation of ascitic fluid in obstruction of the portal circulation or of the inferior vena cava.

It must be remembered, however, that the protein content of hydrocephalic fluid as compared with ascitic or other serous fluids is a very low one.

THE ANATOMICAL FACTORS CONCERNED IN THE PRODUCTION OF HYDROCEPHALUS

It will be unnecessary to recapitulate here the excellent descriptions of the choroid plexuses and membranes of the brain and spinal cord which are to be found in the voluminous literature dealing with hydrocephalus and the cerebro-spinal fluid and in the classical text-books of Anatomy, most of which are based on the original accounts of these parts by Magendie, Luschka, Axel, Key and Retzius, and on the more recent works of such authors as His, Mott and Weed. There has, however, been a considerable difference of opinion with regard to the presence of foramina in the pia-ependymal roof of the fourth ventricle; the exact relations of the perivascular spaces of Robin; the nature of the arachnoid villi and Pacchionian bodies; and the existence of capillaries in the pia mater. We have therefore devoted a considerable amount of time to the study of these debatable points, which we have approached from the embryological standpoint in addition to making observations on the structure of these parts in the adult. The existence of the median aperture at the lower angle of the fourth ventricle has been doubted and actually denied by Cruveilhier, Reichert, Kölliker and others, and in our own country by the late Professor Cleland and others, who believe that the opening is an artefact, caused by traction on the medulla oblongata either in the removal of the brain, or by separating the medulla from the inferior vermis of the

cerebellum. Thus Professor Cleland in 1896 stated that "the fourth ventricle cannot be opened by separation of the medulla oblongata from the cerebellum without injury to the pia mater. It is a mesial tear made in this way below the extremity of the choroid plexus which is described by Luschka under the name of foramen of Magendie and is figured by most recent writers, and supposed by them to be natural. It can easily be demonstrated to be artificial, if the dissector be on his guard; but it is not easy to make certain if there is within the circuit of the choroid plexus a layer independent of the proper investment of the uvula and nodule."

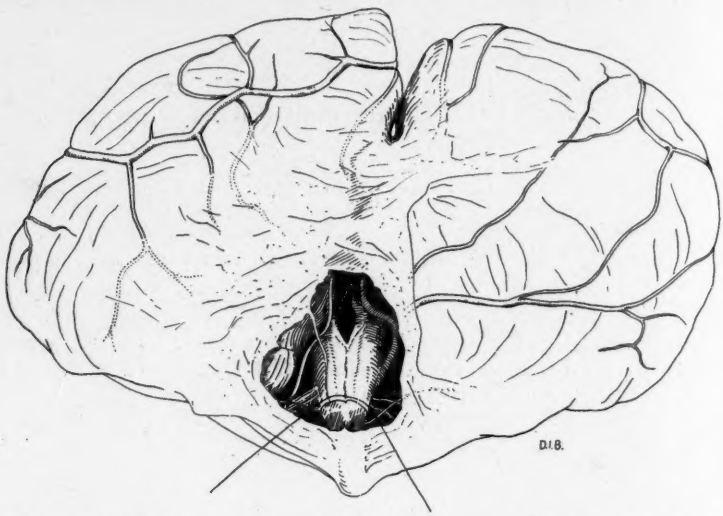


Fig. 6. Cerebellum and medulla oblongata viewed from above and behind. The arachnoid membrane has been opened so as to expose the cisterna magna (cisterna cerebello-medullaris), and the lower part of the medulla has been retracted and held in position by a thread. A large median aperture is present in the tela choroidea inferior, with smooth rounded edges. The space is traversed by thin strands of pia arachnoid, and by blood vessels and nerves.

We have carefully examined a considerable number of brains with the object of determining whether these foramina are produced by tearing or exist as natural openings; and we have no doubt whatever that the foramen of Magendie does normally exist as a natural opening in the lower part of the roof of the fourth ventricle, figs. 6 and 7, and also that the foramen of Luschka, through which a lateral tuft of the choroid plexus projects, on each side, beneath the flocculus, is also a natural opening. This is limited below by a smooth untorn edge, which is the crescentic free border of a membrane which forms its lower boundary; and it is limited above by the flocculus and the posterior medullary velum, fig. 7.

The part of the sub-arachnoid space, into which this tuft of choroid plexus projects, is usually distinguished by the term *cisterna lateralis*. Should adhesive meningitis seal its outlets into the ventricle and sub-arachnoid space, a cyst results, compressing the VIIth and VIIIth cranial nerves, and so producing Bárány's syndrome.

The foramen of Magendie may be exposed, in the ordinary way from behind, by cutting through the arachnoid membrane which forms the roof and posterior wall of the cisterna magna, fig. 6. On raising the membrane, the observer may, if the foramen is a large one, look directly into the fourth ventricle. The opening in certain cases in which it is very large is bounded below by the upper

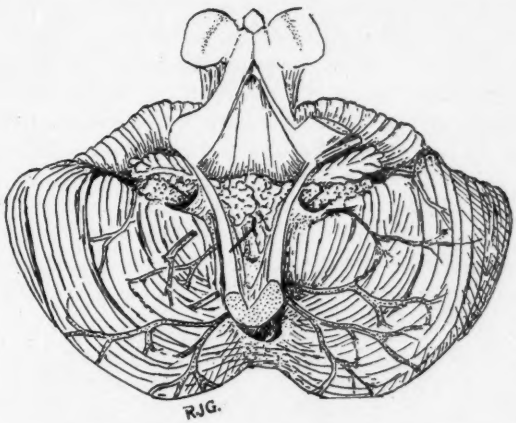


Fig. 7. Drawing of the roof of the fourth ventricle which has been exposed by removal of the pons Varolii, and ventral part of the medulla oblongata. The median opening of Magendie which lies near the lower angle of the ventricle below the choroid plexus is indicated by a bristle passing through it into the cisterna magna. The lateral openings of Luschka are also exposed and a small tuft of the choroid plexus, the "cornucopia," is seen projecting through the opening. This is bounded in front by the flocculus, behind by a crescentic fold formed by pia mater lined internally by ependyma.

edge of the obex, and more laterally by the ligulae; above it is limited by the choroid plexus, which is inflected into the lower part of the ventricle. If of small size the opening is seen to be medial in position. It lies beneath the nodule and uvula and in the narrow interval between the two tonsillar lobes. It has well-defined, symmetrical, even borders, and it is hardly conceivable that these represent the edges of a recent tear. The opening is in the lower part of the pia ependymal roof of the ventricle, which membrane is distinct from the pia mater covering the under surface of the inferior vermis. The doubt as to whether these two membranes are independent, which was expressed by Cleland, may, we think, be explained by assuming that the two layers may

become adherent as the result of a localised meningitis, and that the presence of adhesions produced in this way may have been responsible for Cleland's statement that "the fourth ventricle cannot be opened by separation of the medulla oblongata from the cerebellum without injury to the pia mater."

In order to make certain that the openings were not produced by tearing, we exposed the roof of the ventricle from the ventral aspect by carefully removing the pons Varolii and upper part of the medulla oblongata, fig. 7. This method of dissection gives an excellent view of the lateral and median apertures and also of the recessus tecti and choroid plexuses, and entirely disposes of the theory that the openings are produced by traction.

Around the margins of the foramen of Magendie large vessels are seen to lie in the sub-arachnoid space. These are branches of the posterior inferior cerebellar arteries together with corresponding veins. Numerous delicate trabeculae of connective tissue bridge across the cavity of the cistern. The discovery by Magendie of the median aperture known by his name, was recorded by him in 1826 in the following words: "Alors j'incisai la dure-mère, et l'arachnoïde du cou, et je mis à découvert la fin du quatrième ventricule, c'est-à-dire, le point où pouvait se rencontrer la communication avec les cavités du cerveau. Dans cette position je pouvais facilement juger du fait que m'intéressait; je n'avais qu'à exercer une légère pression sur le cerveau. Si la communication existait, le liquide devait couler vers la cavité de l'arachnoïde de l'épine. C'est ce dont je pus aisément me convaincre ainsi que les personnes qui m'assistaient. Chaque fois que je me comprimais même, le plus légèrement possible, les hémisphères du cerveau, il s'écoulait une eau limpide par une ouverture placée immédiatement au devant de la fin du quatrième ventricule, à cet endroit que les anatomistes ont appelé, le bec de la plume."..."Je donne donc comme une disposition anatomique constante, et facile à vérifier, que le quatrième ventricule communique librement avec la cavité spinale sous-arachnoïdienne: la communication est établie par une ouverture arrondie placée entre les deux artères cérébelleuses postérieures, et qui a de deux à trois lignes de diamètre. Je l'ai vue plusieurs fois beaucoup plus grande encore: sa partie supérieure et latérale est formée par les nombreux vaisseaux sanguins de la pie-mère, qui se rendent au cervelet, et aux plexus choroïdes de cet organe. Latéralement et au-dessus des vaisseaux ce trou est formé par la partie interne de la lame cornée médullaire qui borde sur les côtés et en bas le quatrième ventricule. En bas il est terminé par le bec de la plume lui-même"..."j'ai vérifié par plus de quarante autopsies...." It may be noted here that John Hilton in his classic work upon *Rest and Pain*, wrote in reference to this controversy: "The existence of this cerebro-spinal aperture ...is not perhaps universally admitted, but I believe beyond all doubt that it is the normal arrangement of structure that there should be such an aperture. Some years ago I took a great deal of trouble for the purpose of ascertaining this point in a very exact manner, and in no one instance except where there were abnormal collections of fluid in the brain did I find this aperture wanting."

Hilton was also the first to draw attention to the effect of occlusion of the cerebro-spinal openings in the production of hydrocephalus.

The foramina in the roof of the fourth ventricle are described as being occasionally absent. Retzius found the foramen of Magendie present in 98 out of 100 brains, and the foramina of Luschka in 195 out of 200, or 97·5 per cent. of the cases examined(17). We have so far been unable to confirm the description by Merkel and Mierzejewsky of a foramen establishing a communication between the descending horn of the lateral ventricle, and the sub-arachnoid space. This foramen was supposed by these authors to be a deficiency

Fig. 8. Section through the tuft of choroid plexus which projects through the foramen of Luschka into the cisterna lateralis of the sub-arachnoid space.

in the pia ependymal wall at the lower extremity of the choroidal fissure of the cerebrum. Should such a foramen exist it must be supposed that it is incapable, together with its fellow of the opposite side, of permitting adequate escape of the ventricular fluid, in cases of hydrocephalus due to obstruction of the foramina of Luschka and of Magendie; for it can hardly be supposed that in all cases of obstructive hydrocephalus, the five foramina would be simultaneously obliterated. The same criticism applies in the cases described by Dandy, as communicating hydrocephalus; adhesions around the mid-brain would not cut off the foramina of Merkel and Mierzejewsky from the great absorptive area of the vault.

Although the sub-arachnoid spaces in the position of the cisternae are large, there is very little space between the arachnoid and pia mater on the surface of the cerebral hemispheres and over the cerebellum. Over the summits of the gyri the arachnoid is strongly adherent to and indistinguishable from the pia mater, so that the "circulation of the cerebro-spinal fluid" must take place chiefly in the sulci, and there is normally very little room for the accumulation of cerebro-spinal fluid in the sub-arachnoid space, outside the brain. Any large quantity of fluid outside the brain, such as is seen in general atrophy with diminution in size of the brain, or in external hydrocephalus, will be situated partly in the sub-dural space.

The anatomical relations of the pial and arachnoid membranes differ considerably in the cranial cavity and the vertebral canal. In the latter there is a considerable space beneath the arachnoid membrane, and between it and the pia mater covering the spinal cord. This space, which is traversed by the roots of the spinal nerves, including those forming the cauda equina, extends to the level of the second or third sacral vertebra. Externally, in the region of the spinal cord, the arachnoid is in close contact with, and is firmly supported by, the dura matral sheath, which is a tough unyielding membrane. There is thus very little space outside the brain and spinal cord for the accommodation of additional fluid in cases of hydrocephalus, for in the skull the convolutions of the brain covered by the pia-arachnoid membrane are normally in contact with the dura mater lining the cranial cavity and obviously no appreciable enlargement of the brain can take place without expansion of the skull; and since the sub-arachnoid space of the spinal cord is already filled with fluid, which is confined within a strong tubular sheath of dura mater, any increase in the pressure of the cerebro-spinal fluid within the ventricles will be resisted by the pressure of the fluid in the sub-arachnoid space. Moreover, if there should be an interference with the normal absorption of cerebro-spinal fluid into the venous sinuses, it is obvious that, owing to the resistance offered by the sub-arachnoid fluid outside the brain and spinal cord, an internal hydrocephalus could develop without any obstruction taking place at the foramina in the roof and lateral angles of the fourth ventricle. This deduction is supported by the fact that in a large number of cases of internal hydrocephalus, the fourth ventricle, and the central canal of the spinal cord remain undilated. Moreover, in a considerable number of cases of congenital internal hydrocephalus which have been treated by lumbar puncture, the withdrawal of cerebro-spinal fluid from the sub-arachnoid space of the spinal cord, has been attended by depression of the anterior fontanelle, indicating that there has been an escape of cerebro-spinal fluid from the ventricles of the brain into the sub-arachnoid space. Cushing also has recorded cases in which when a needle attached to a manometer was inserted through the bulging fontanelle into the ventricle, and another in the lumbar sac, the pressure level of the fluid in both usually remained the same and fluctuated equally with crying, straining, or jugular pressure as well as on withdrawal of fluid from either end of the system.

In any consideration therefore of the causes of hydrocephalus, the relation between the pressure of the cerebro-spinal fluid within the ventricles and sub-arachnoid spaces and of the blood in the venous sinuses of the dura mater is of cardinal importance. It has been stated by Leonard Hill in 1909(13) that these are one and the same. It must be assumed, however, that if the fluid is secreted by the epithelium covering the choroid plexuses, and absorbed into the venous system, that there must be a circulation of the cerebro-spinal fluid from the ventricles through the foramina of Magendie and Luschka into the sub-arachnoid space, and from this to the venous system. Moreover, if we admit that such circulation of the cerebro-spinal fluid exists, it follows that, although the differences in pressure may be slight and difficult to detect, there must necessarily be a higher pressure in the ventricles than in the sub-arachnoid space, and excluding osmotic influences, the pressure of the cerebro-spinal fluid in this space must be greater than that in the intracranial venous sinuses.

The amount of cerebro-spinal fluid secreted in an adult human subject in 24 hours is difficult to ascertain, as the withdrawal or escape of fluid alters the normal conditions; it has been stated to be not less than 500 c.c., there being a continuous secretion and absorption of the fluid throughout life. Macleod gives the normal quantity of cerebro-spinal fluid secreted in 24 hours as 60–80 c.c. Possibly the atrophy of the brain in old age and the resulting hydrocephalus *ex vacuo* are responsible for the more generous estimates of certain authors. It has been stated that absorption occurs after death and that none remains 70 hours after this event. In fractures of the base of the skull the cerebro-spinal fluid may drain away at the rate of 200 c.c. a day or more, and it has been recorded that in a case of cerebro-spinal rhinorrhoea as much as 700 c.c. of cerebro-spinal fluid have escaped in a single day. Billroth has recorded 1–2 litres! This, however, does not imply that the daily amount of cerebro-spinal fluid secreted under normal circumstances is as high as 200 c.c. or more, as if the cerebro-spinal fluid is able to escape readily, the pressure will obviously be lowered, and the resistance being lessened, presumably an increase in the amount of secretion would take place. Moreover, some of these cases are complicated by meningitis, and in these fluid may be exuded from the vessels independently of a true secretion of cerebro-spinal fluid.

In cases of obstructive hydrocephalus, either intra-ventricular or extra-ventricular, the pressure of the cerebro-spinal fluid is raised up to a point at which the resistance is sufficiently great to retard or prevent for the time any further secretion, and it is quite possible that the daily output of cerebro-spinal fluid would be even less than normal. The condition being this, that less is excreted or drained away, and that owing to increase in pressure caused by the obstruction to its escape less is secreted. The whole question of the relation of the intra-ventricular and extra-ventricular pressure of the cerebro-spinal fluid to its secretion and absorption has been ably treated by Hill, Cushing, Weed and McKibben, Nañagas and others. (1) It has been shown

that the pressure of the cerebro-spinal fluid is influenced by the blood pressure and respiration; being increased by an augmentation in the pressure of the blood in the venous sinuses, and diminished by a lowering of the pressure in these sinuses. (2) It is increased by the injection of irritant substances such as lamp-black into the ventricles or sub-arachnoid spaces, which produce an inflammatory reaction of the meninges followed by an increase of fluid in the ventricles of the brain, or what is known as an "artificial hydrocephalus." The latter condition is said to be due to the blocking of the pathways of absorption through the sub-arachnoid spaces, through the arachnoidal villi into the venous sinuses, or to blocking of the foramina of Magendie and Luschka by plastic meningitis (Nañagas(23)). (3) A temporary increase in the pressure of the cerebro-spinal fluid may also be obtained by the injection of hypotonic salt solutions or distilled water into the venous system, which presumably acts by preventing the passage by dialysis or filtration of the cerebro-spinal fluid from the sub-arachnoid space into the venous system, or by increased secretion by the choroidal epithelium, since changes have been observed in this epithelium after the injection of hypotonic fluid into the venous system. A third factor, swelling of the brain, has to be taken into account (Weed). In contrast with the foregoing the pressure of the cerebro-spinal fluid may be temporarily lowered by the injection into the venous system of hypertonic saline solutions; e.g. the injection of a 30 per cent. solution of sodium chloride into a superficial vein, or the administration of a similar solution by mouth or injection into the intestine. (4) An increase of the pressure of the cerebro-spinal fluid has also been produced by ligature or compression of the vena magna Galeni. (5) There may also be, as has been shown by Dixon and Halliburton(8), an increased output of cerebro-spinal fluid such as that produced by the intravenous injection of a saline extract of choroid plexus, or of brain extract, or by the action of an anaesthetic such as ether. Among other substances which stimulate the action of the "choroid glands" may be mentioned theobromine and muscarine[1]. As a result of stimulation with ether or muscarine Pettit and Gérard have shown in the dog, rabbit and guinea-pig that the cells of the choroidal epithelium are increased in size so that their height is nearly doubled and the secretory globules are greatly increased in number.

Intracranial pressure.

Hill's statement that the "brain-pressure," the cerebro-spinal fluid pressure and the venous pressure are one and the same is hardly tenable in the light of more recent investigations(14). There can be no doubt that the sub-arachnoid pressure is normally higher than the venous pressure, though lower than the cerebral capillary pressure, as may be seen from the following table:

Arterial pressure	Capillary pressure	Venous pressure	C. S. F. pressure	Salivary pressure
mm. H_2O, 1300	200–270	45 or less	60–120	1800

[1] Pettit and Gérard, quoted in Mestrezat, *Le Liquide Cephalo-Rachidien*, p. 61.

Mere filtration would therefore adequately account for absorption of cerebro-spinal fluid into the venous sinuses, whereas should absorption into capillaries be hypothecated the aid of other factors such as osmosis and secretion has to be invoked.

Hill also believed that no pathological increase of intracranial tension could be transmitted to the cerebro-spinal fluid. Clinical evidence in some cases would appear to support this view. Many cases of cerebral tumour with marked papilloedema and severe headache, when lumbar or cistern puncture is performed show no increased tension of the escaping fluid. In others, however, the classical cases, the increase is so marked that the fluid escapes from the cannula in a horizontal stream. It would appear that there is either a greater margin of absorptional capacity in some individuals than in others, or that in some, choked disc results from a lower intracranial tension than in the majority. It is not known how far a cerebral tumour can encroach on the space normally occupied by the cerebro-spinal fluid before the pressure rises. It would seem as if in some cases the choroid plexuses secreted more fluid in response to the stimulus of rising tension. On the other hand, the relation of cerebral tumour to internal hydrocephalus is a simpler one; the tumour either compresses the aqueduct of Sylvius, blocks the roof foramina, or else obstructs the vein of Galen.

It has been postulated that a continuance of a direct relationship between arterial and cerebro-spinal fluid pressures accompanies the rising arterial tension of advancing years (18). In our experience this has not been adequately confirmed, for while in some cases high arterial pressure is undoubtedly paralleled in the cerebro-spinal fluid, other examples unaccompanied by such increase could be pointed out. Should such a relation exist, it is probably an indirect one, through the medium of the choroid plexus, though it is possible that the atheromatous process might interfere with escape of fluid through arachnoidal villi into the venous sinuses: cases of endophlebitis of the sagittal sinus, usually syphilitic, are known, and though they usually culminate in thrombosis, there must be a period prior to this disaster in which the arachnoidal villi are liable to be plugged with inflammatory products.

Le Gros Clark (18) suggested that the increased vascular tension of advancing years might thus be the indirect source of the progressive elaboration of the Pacchionian bodies in older people. He invoked a similar explanation for their increase in number in certain diseases, notably dementia paralytica, in which the intracranial pressure, though not necessarily the blood pressure, is supposed to be raised. The Pacchionian bodies, however, undergo a considerable increase during that period of life during which there is no great rise of intra-vascular tension, and in many cases of general paralysis no increase of cerebro-spinal fluid pressure can be demonstrated with an ordinary manometer attached to the lumbar-puncture needle.

Secretion of the Cerebro-spinal Fluid.

Several direct observations of secretion of cerebro-spinal fluid have been made. Thus Cushing quotes, as examples of this, Mott's cases (22): "On two or three occasions I have had the opportunity in man to observe the main plexus at the bottom of a large porencephalic cavity emptied of its contents, and have seen the fluid exuding from the surface of the structure. In one such case associated with apparent occlusion of the foramen of Monro, the plexus was removed, and in another the entering vessels were ligated, with immediate cessation of secretion. These patients were under ether anaesthesia and inhalation anaesthetics, as others have pointed out, and we also have observed, are among the few substances which definitely activate choroidal secretion." Cushing himself (5) records a case of unilateral hydrocephalus due to a cystic tumour which occluded the right foramen of Monro. The ventricle was opened and the choroid plexus exposed. Fluid was seen to exude freely from its surface. On clamping the choroidal artery the organ became blanched and secretion apparently ceased.

It will be unnecessary here to do more than allude to the more recent experimental work and observations on the function of the "choroidal glands."

Dandy and Blackfan (7), experimenting on dogs, showed that occlusion of the foramen of Monro, by the insertion of a strip of fascia or peritoneum, was followed by dilatation of the corresponding ventricle; and further that excision of the choroid plexus resulted in collapse of the ventricle. They also blocked the aqueduct of Sylvius with an oiled gelatine capsule containing wool; this was likewise followed by a dilatation of the third and both lateral ventricles. Moreover, after obstructing the iter, he removed the choroid plexuses from both lateral ventricles, leaving the choroid plexus of the third ventricle; this resulted in a slight degree of dilatation of the lateral ventricle on each side owing to continued secretion of cerebro-spinal fluid by the choroid plexus of the third ventricle.

The effects of pathological obstruction of the iter or foramina in the roof of the fourth ventricle are so well known that it is only necessary here to mention this most important cause of internal hydrocephalus as additional evidence in favour of the source of the cerebro-spinal fluid being the choroid glands.

Mott has demonstrated the presence of secretory granules in the cytoplasm of the choroidal epithelium, and of cup-shaped vacuoles in the situations whence such granules have been discharged.

Mott (22), Huber (16), Hunter and others, moreover, have shown, by the use of methylene-blue, the presence of nerve fibres on the vessels of the choroid plexuses, and other regions of the pia mater. Mott stained with methylene blue small portions of choroid plexus excised immediately after death, while Huber injected the dye into the vascular system during life. Huber described two types of nerve fibres forming plexuses on the pia mater, (1) medullated

and (2) non-medullated. (1) The medullated fibres showed definite nodes of Ranvier, and for the most part, after having lost their myelin-sheaths they terminated in the adventitia in a network of fine varicose fibrils; some of these appeared to reach the muscular coat and endothelium, but they were difficult to trace. (2) Non-medullated fibres of the sympathetic formed fine plexuses from which slender varicose fibrils passed between the cells of the unstriped muscle of the tunica media. These were considered to be vaso-motor in function, whereas the medullated fibres were regarded as afferent in nature.

Thus, whilst the cerebral arteries are relatively poor with regard to the amount of unstriped muscular tissue in their walls (fig. 9, *A* and *B*), it must be remembered that not only have afferent fibres been described as ending in

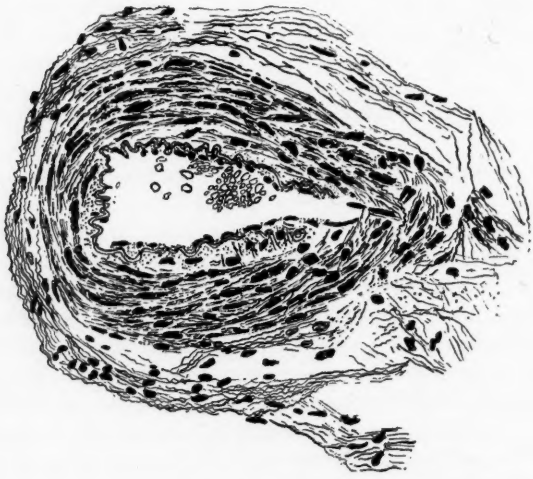
A

Fig. 9. Cross-section of the middle cerebral artery.

their adventitial coats, but also efferent fibres have been traced to the media (Huber (16)). Such nerve fibres must transmit impulses and, it may be inferred, cause a certain amount of vaso-constriction to take place when the need arises. Moreover, it is evident that the principal effects of such constriction would be most easily recognisable in the general arterial pressure, as it is difficult to measure the venous outflow from the skull cavity owing to the numerous exits. Nevertheless Wiggers found when he perfused the cerebral arteries with oxygenated Locke's solution a certain amount of blood escaping from the sinuses was measurable; on addition of adrenaline to this solution there was a definite, if not large, diminution in the outflow. It seems probable therefore that a slight but quite definite constriction of cerebral arteries had occurred, and that there is a vaso-motor mechanism available for the brain. Owing to

B

Fig. 9. Cross-section of a small artery in the sub-arachnoid space.



C

Fig. 9. Cross-section of an artery from the tonsil; for comparison with *A* and *B* to show the relative amounts of muscle in the tunica media.

the rigidity of the cranial wall it is possibly mainly a differential one, the vessels of one area experiencing a vaso-dilatation while adjacent vessels suffer a relative constriction.

Clinicians have often invoked such an arrangement. Migraine has often been attributed to vascular disturbances, the feeling of well-being which precedes the attack being supposed to result from a dilatation of vessels, the ensuing pain and visual abnormalities from a subsequent constriction. The

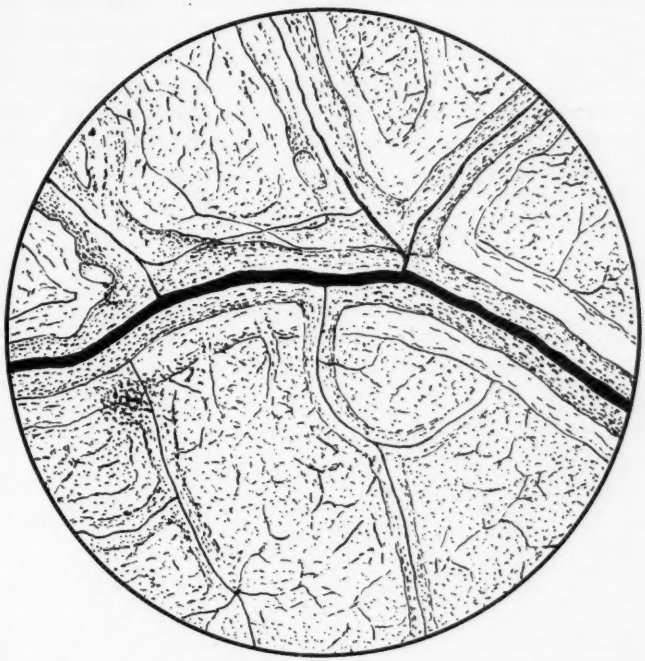


Fig. 10. Vessels in a film preparation of the pia mater of a cat. The specimen was stained with gold chloride. The vessel walls are strongly contracted, and their lumina, shown black, are much reduced in size. In the larger vessels a considerable space is visible between the vessel wall and the surrounding tissue. This is probably due to the contraction of the vessels produced by the action of the formic acid employed in the preparation of the specimen.

attacks of dizziness occasionally met with in hyperpiesia are frequently attributed to spasm of cerebral arteries; dizziness is, however, commoner with abnormally low blood-pressures.

As Dixon and Halliburton suggested, absolute variation in the volume of cranial blood can occur at the expense of the cerebro-spinal fluid (8). More recently Weed and McKibben found (34) that the volume of the brain varied under different experimental conditions. After intravenous injection of hypertonic solutions the convolutions were shrunken, whereas after injections of

distilled water the opposite effect is found, and the brain has a swollen appearance. Microscopically these swollen brains showed accumulations of fluid in the pericellular spaces. While the exact cause of these phenomena remains obscure, they afford a remarkable confirmation and extension of the views of Dixon and Halliburton.

All observers are agreed that increased velocity of blood through the cerebral vessels is probable when the general blood pressure is raised; this would exert an influence on the activity of the choroidal epithelium.

The degree to which the vessels of the pia mater are capable of contracting will be realised by a glance at the arterioles depicted in fig. 10, which represents a film preparation of the pia arachnoid of a cat, stained immediately after death with gold chloride after fixation with formic acid. The excessive contraction is shown firstly by the marked shrinkage of the arterial wall from its investing sheath, and secondly, by the very marked reduction of the lumen.

(To be continued)

THE INSERTION OF THE PECTORALIS MINOR MUSCLE

By J. M. YOFFEY, M.B., Ch.B., B.Sc. (Manch.)

The tendon of the lesser pectoral muscle, in so far as its attachment to the coracoid process is concerned, is usually described simply as being inserted on to the process, no mention being made of the fact that this insertion produces any marking on the bone. A recent study has demonstrated the fact that usually a distinct marking defines the attachment of the muscle to the coracoid process. This marking may take the form of a sharp ridge, or a slightly roughened tubercle, but more often a combination of the two. Out of 115 scapulae examined in the Anatomical Department of Manchester University, 87 per cent. showed this marking, of which the subjoined photograph represents a typical specimen.

I am indebted to Professor J. S. B. Stopford for his kind permission to examine the requisite material in the Anatomical Department of Manchester University.

REVIEW

Baillière's Synthetic Anatomy: A Series of Drawings on Transparent Sheets for facilitating the Reconstruction of Mental Pictures of the Human Body. By J. E. CHEESMAN. Part I, The Shoulder and Arm. 12 Plates. Part II, The Forearm. 12 Plates. Part III, The Hand. 12 Plates. London: Baillière, Tindall and Cox, 1926. Price per part, 2*s.* 6*d.* net.

It is generally agreed that the only satisfactory method of acquiring a knowledge of the subject of Human Anatomy is by careful and thorough dissection of the cadaver. Many students, however, find that dissection alone is insufficient to enable them to retain the knowledge so acquired, and they have recourse to additional methods. The book under review provides a new method and one which is intended to help the student in the revision of his work, after the completion of his dissections. It consists of coloured plates, printed on transparent paper, and all drawn to the same scale, so that they may be superimposed on one another.

The Upper Limb is divided into three parts: (1) the shoulder and arm, (2) the forearm, and (3) the hand. There are twelve plates in each part, six depicting successive dissections from in front and six from behind. The first plate in each half of each part shows the skin, with the appropriate surface elevations and depressions, and this can be superimposed on one or more of the deeper dissections.

The idea is excellent and certainly from the point of view of surface anatomy, the book will prove helpful to the student and valuable to the teacher. The author believes that the co-relation of the deeper dissections with one another will also prove of value, but the practical difficulties with which this method is faced are almost insuperable. The difficulty of ensuring accurate printing of the colours is of little importance in regions where the vessels and nerves are not crowded together, but inaccuracy in the colour printing in such a region as the axilla cannot but complicate a picture which is of necessity far from simple, and detracts from the benefit to be derived by superimposing one plate on another.

The author is to be congratulated on the anatomical accuracy of the figures and on the ingenuity which he has displayed throughout the work. Such inaccuracies as do occur are of relatively little importance, although the omission of the bicipital fascia (*lacertus fibrosus*) from the arm section is a little surprising.

As an aid to the study of Surface Anatomy, the plates should be welcomed, and the publication of the subsequent parts, which are to treat the rest of the body in the same way, may be awaited with interest. Each part has its own index, conveniently arranged so as to be accessible at once without the necessity of turning over pages. The plates, when completed, can all be contained in the one cover, and the publishers merit congratulation on the way in which the work has been presented.

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